Division of

Cancer Etiology

1988 Annual Report
Intramural Activities
Volume III

October 1, 1987
September 30, 1988

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OF HEALTH
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ANNUAL REPORT

DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

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ANNUAL REPORT OF

THE EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

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The Epidemiology and Biostatistics Program is the focus within the Institute for epidemiologic and biostatistical research in cancer etiology. The Program is responsible for intramural, collaborative, and grant-supported investigations into the distribution, causes, natural history, and means of prevention of cancer. The Program employs epidemiologic approaches that are comprehensive and cover the gamut of environmental and host determinants of cancer. The Program also conducts and supports the development of new methodologic approaches in epidemiology and biostatistics, multidisciplinary investigations combining epidemiologic and laboratory methods, and biostatistical and mathematical research on carcinogenic mechanisms and risk assessment.

Dr. Joseph F. Fraumeni, Jr. continues to direct the Program as the Associate Director for Epidemiology and Biostatistics. No major organizational changes occurred during the year, although the Program moved offices from the Landow Building in Bethesda, Maryland to Executive Plaza North, located in Rockville, Maryland. The five components of the Program are the Biostatistics Branch (Chief, Dr. William J. Blot), the Environmental Epidemiology Branch (Chief, Dr. Robert N. Hoover), the Clinical Epidemiology Branch (Chief, Dr. Robert W. Miller), the Radiation Epidemiology Branch (Chief, Dr. John D. Boice, Jr.), and the Extramural Programs Branch (Chief, Dr. John A. Cooper). Formal site visits to the Biostatistics and Environmental Epidemiology Branches took place during this year. The research and other activities of each Branch are described in the sections following this report, which focuses on the orientation, highlights, and direction of the overall Program.

Intramural Research

Continued emphasis was given to case-control and cohort studies evaluating key hypotheses in cancer etiology. Case-control studies of selected cancers were undertaken when high-risk communities were identified on the cancer mortality maps, major hypotheses were testable, or special resources became available. Laboratory methods were often incorporated into studies to help clarify exposures, preclinical responses, and mechanisms of carcinogenesis.

Some descriptive surveys were also undertaken. In particular, an updated atlas was published to illustrate the geographic patterns of cancer mortality by state economic area in the 1970s. When comparisons were made to patterns in the two earlier decades, the most striking changes were the emergence of elevated mortality from lung cancer among women in areas of Florida and along the west coast, and from non-Hodgkin's lymphoma among residents in the central states, especially Kansas. Most other cancer sites in the 1970s showed similar patterns as before, although there was a general trend towards geographic uniformity over time. A similar trend is seen for non-whites in a companion atlas that is nearing completion. The most striking change among non-whites

was the recent emergence of elevated rates for prostate cancer along the South Atlantic coast. A detailed report on time trends in cancer incidence and mortality rates at the national level was published, revealing remarkable increases in lung cancer, skin melanoma, multiple myeloma, and non-Hodgkin's lymphoma.

Tobacco and alcohol: Tobacco habits and lung cancer risks vary geographically in the United States. A previous case-control study of lung cancer in a high-risk area of southern Louisiana implicated the heavy use by Cajuns of local brands and hand-rolled cigarettes containing high-tar levels. This year, a case-control study of pancreas cancer revealed an excess risk among Cajuns, which was partly associated with smoking habits but not with alcohol intake. Several case-control studies evaluated the possible association of lung cancer with passive smoking. In Shanghai, the risks among nonsmoking women tended to rise with increasing years lived with a smoking husband. These findings resemble those of earlier Program studies of lung cancer among nonsmoking women in the United States and Japan, whose risk increased in proportion to the number of cigarettes their husbands smoked.

Tobacco and alcohol were identified as the primary risk factors in case-control studies of esophageal, oral, and laryngeal cancers. In a study of esophageal cancer in coastal South Carolina, nearly 90% of the black male cases reported the consumption of moonshine whiskey, which seemed to contribute to the longstanding elevated rates of this cancer among blacks in this area. In a large multicenter study of oral and pharyngeal cancer, it was possible to show alcohol consumption as an independent risk factor among lifelong nonsmokers. Tobacco and alcohol appeared to combine in a multiplicative fashion in enhancing oral and pharyngeal cancer risk, with over a 35-fold excess risk among heavy smokers and drinkers. In a study of laryngeal cancer in coastal Texas, smoking was the major risk factor, combining with alcohol intake in a manner intermediate between additive and multiplicative models.

Occupation: Most chemicals known to be human carcinogens were first identified in studies of occupational groups, whose exposures are heavier and of longer duration than typically found among the general population. Studies in the workplace continue to provide opportunities to identify and clarify environmental causes of cancer. Although occupational investigations are underway on a wide range of exposures, recent studies have focused on pesticides, formaldehyde, organic solvents, organic and inorganic dusts, and metals. Of growing importance are projects to improve exposure assessment procedures, evaluate dose-response patterns, and develop new resources for occupational studies, such as a referent data base composed of a worker population.

Last year, an NCI study of farmers in Kansas noted a provocative association between non-Hodgkin's lymphoma and exposure to pesticides, especially phenoxyacetic acid (2,4-D). This year, a study of agricultural extension agents, exposed to pesticides while conducting demonstration projects for farmers, revealed an excess of leukemia. Preliminary data from a case-control study in Iowa and Minnesota showed elevated risks for chronic lymphatic leukemia and non-Hodgkin's lymphoma among farmers using pesticides such as DDT, malathion, dieldrin, lindane, carbaryl, choramben, and 2,4,5-T, particularly if use occurred 20 or more years before interview. Cohort mortality studies of pesticide applicators employed by a national lawn care company and by county

noxious weed departments, and a case-control study of lymphatic and hematopoietic cancer are underway to clarify associations between pesticide exposure and cancer.

A large case-control study of brain cancer conducted in Pennsylvania, New Jersey, and Louisiana uncovered excess risks among persons employed in the electrical and electronics industries, particularly in jobs with exposure to chemical solvents. The risk of astrocytic brain cancer rose with duration of employment or repair of electronic equipment to 10-fold among those employed at least 20 years. No significantly elevated risks of brain cancer were associated with employment in the chemical industry, although there were slight excesses among persons with exposure to cutting fluids, organic solvents, or among those employed in the petroleum industry. The relationship between bladder cancer and employment in the chemical industry was assessed in data from the National Bladder Cancer Survey. Employment in the production of organic chemicals was associated with a 1.3-fold excess risk among men, increasing to 2.4-fold among those employed for 20 years or more. Excess risks were also seen in the plastics industry and in the production of agricultural chemicals, especially in the pesticide subdivision.

The carcinogenicity of formaldehyde in laboratory animals and its widespread use in industrial processes and commercial products prompted several epidemiologic studies. A case-control study in Connecticut noted an excess of nasopharyngeal cancer, but not sinonasal cancer, among persons holding jobs where contact with formaldehyde may have occurred. Risks rose to over twofold among those exposed to high levels 20 or more years earlier. These results are consistent with an excess of nasopharyngeal cancer seen in a large NCI cohort study of industrial workers exposed to formaldehyde.

In a case-control study of laryngeal cancer in coastal Texas, analysis of occupational histories revealed excess risks in the transportation, metal fabricating, construction, and maintenance industries, as well as in workers exposed to asbestos, paint, and diesel or gasoline fumes.

In China, cohort investigations were begun to evaluate cancer risks among 100,000 workers exposed to varying levels of benzene; 80,000 workers with potential for silica exposure, including over 5,000 with silicosis; and over 20,000 tin miners, many of whom are highly exposed to radon and inorganic arsenic beginning at very young ages. The large size of these studies will enable improved assessment of carcinogenic risks, including dose-response patterns.

In collaboration with Swedish investigators, utilizing linked census and cancer registry data, several new etiologic leads were reported this year: bladder cancer among pulp and fiberboard workers and rope and twine makers, and among dental technicians; multiple myeloma among bath and swimming hall workers exposed to ortho-toluidine; malignant melanoma among printers; and male breast cancer among soap and perfume workers involved in the formulation of estrogen-containing beauty creams.

Radiation: Studies continued to investigate the relationship between cancer risk and ionizing radiation, and especially to improve estimates of risk associated with low doses. Better data on low level effects are needed to base regulatory and other decisions about the potential hazard from medical,

occupational and environmental exposures, and to assess the value of exposure avoidance as a means of cancer prevention.

A new survey of breast cancer among women treated for scoliosis revealed elevated risks following an average of 40 x-rays to the spine to monitor curvature. Most of the exposures occurred during childhood or adolescence, suggesting that the developing breast is especially susceptible to the carcinogenic effects of radiation. A case-control study of breast cancer among atomic bomb survivors found that risk appeared greater among women who became pregnant after exposure. In a case-control study of thyroid cancer in Connecticut, pregnancy enhanced the risk of this cancer among women irradiated in the head and neck region as children.

A study of adult leukemia and lymphoma utilizing prepaid health plans indicated that diagnostic x-rays may not be causally related to these diseases, but simply associated with conditions that portend their development. Low doses of diagnostic 131-iodine were not found to increase the risk of thyroid cancer in over 35,000 patients in Sweden, indicating that the carcinogenic potential of this exposure is much less than that of x-rays or gamma rays. For the first time, an excess of breast cancer was suggested among German patients treated with 224-radium.

In an international survey of cervical cancer, radiotherapy was found to be associated with a small, but significant risk of leukemia. The risk increased with increasing radiation dose, but decreased at the highest doses. This pattern is consistent with experimental data, suggesting the downturn in risk at high doses is due to cell killing. Adrenal damage by radiation may have contributed to the low breast cancer risk seen even among postmenopausal women and to the correlation with low levels of estrogens and androgens detected in this group. Among women whose ovaries had been removed, there was a suggestion of a dose-response for direct exposure to the breast of about 30 rads on average. An increase of thyroid cancer was noted at 11 rads. Dose-response relationships were reported for 16 cancer sites, including the stomach, uterus, rectum, bladder, vagina, kidney and ovary.

The long-term follow-up of patients who received multiple chest fluoroscopies during lung collapse therapy for tuberculosis has continued. A new survey indicated that repeated, relatively low radiation doses pose some increased risk of breast cancer. The risk appears cumulative, with those exposed during adolescence being especially vulnerable, while women over 40 years of age at exposure were at little or no excess risk. No excess risk of lung cancer was found, despite average cumulative doses on the order of 100 rads, and no consistent dose-response was seen for leukemia. In the Boston area, clinical examination of persons irradiated as children for enlarged tonsils identified an increase in thyroid nodules following doses of the order of 24 rads. However, the risk was much lower than that estimated from a mail survey, suggesting that questionnaire studies might be biased due to extreme under-ascertainment of thyroid disease among non-exposed populations. In southern China, women residing in areas of high natural background radiation due to radioactive monazite sands were not found to have a higher prevalence of thyroid nodular disease than women in neighboring areas. The absence of any differences based upon clinical examination suggests that protracted exposures to very low levels of ionizing radiation throughout life are not associated with thyroid disease. Medical x-ray workers in China were found to have a 50%

higher risk of developing cancer than other specialists, with excesses of leukemia, breast and thyroid cancers.

Among survivors of breast cancer who received radiotherapy, there was a significant risk of developing a second breast cancer. This risk rose with increasing radiation dose to the contralateral breast, although no elevated risk was found among 15-year survivors. Leukemia was not linked to radiotherapy for breast cancer, providing further evidence that cell death predominates over cell transformation when high radiation doses are delivered to limited volumes of tissue. Women irradiated for Hodgkin's disease at a young age were found to be at high risk for breast cancer. Radiotherapy for Hodgkin's disease also appeared to explain the subsequent excess risk of leukemia and cancers of the lung, stomach, bone, and soft tissue. The risk of second cancers of the bone was strongly associated with radiation therapy in an international study of over 9,000 children with cancer.

Special emphasis is being placed on clarifying the role of indoor radon exposure, which may contribute to 9% of all lung cancers in the U.S. based on newly developed risk models utilizing data from earlier NCI studies of uranium miners. More reliable data should come from ongoing case-control studies of lung cancer that involve careful measurements of indoor radon.

The non-neoplastic effects of cancer therapy were examined in two separate series of survivors of childhood cancer. Women who had received radiotherapy to the abdomen for Wilms' tumor had high rates of adverse pregnancy outcomes, not seen in the pregnancies to spouses of male cases. In a five-center collaborative study designed to evaluate the late effects of childhood cancer treatments, both marriage rates and pregnancy rates in survivors were significantly less than controls. More female survivors reached menopause before age 35 than controls. Risks of infertility and early menopause were greatest among survivors treated with alkylating agent chemotherapy or with radiotherapy below the diaphragm. There was no treatment-related excess of birth defects or cancer in the offspring of childhood cancer survivors. Birth defects in the offspring of female survivors with Wilms' tumor appeared consistent with uterine constraint from radiogenic fibrosis, or with the complex of malformations associated with Wilms' tumor.

The effects of ultraviolet (UV) radiation on skin cancer continued to be evaluated. A network of solar UV-B (wavelengths of 290-330 nm) radiation monitors around the country revealed no increases in the amount of radiation reaching the earth's surface since 1974, despite reports indicating recent depletion in the stratospheric ozone and increasing incidence of skin cancers, including melanoma. In assessing the relation of UV-B exposure and skin cancer, new analyses indicate that UV-B is the principal cause, after adjusting for various host and environmental factors. However, the impact (biological application factor) of UV-B on squamous cell carcinoma of the skin is twice as great as for basal cell carcinoma and four times as great as for melanoma. The effects were most pronounced for tumors at exposed sites of the body. In collaboration with the Danish Cancer Registry, a case-control study of melanoma revealed a significant risk associated with leisure-time sun exposure, sun bathing during childhood, fair skin complexion, freckling, and number of nevi.

Medications: Studies were continued to evaluate the carcinogenic effects of cytotoxic drugs, hormones, and other compounds. Alkylating agents used to

treat childhood cancer were associated with an increased risk of bone cancer, providing evidence that solid tumors may result from chemotherapy in long-term survivors. Patients with Hodgkin's disease treated with alkylating agents were found to be at high risk of leukemia, but after 9 years no leukemogenic effect was seen. An increased risk of leukemia and preleukemia was associated with alkylating agent therapy in a case-control study of breast cancer, whereas no risk was apparent following radiotherapy.

Case-control studies revealed an increased risk of invasive cervical cancer associated with oral contraceptives, particularly with long-term use. This risk emerged after adjusting for screening history and persisted after adjusting for other risk factors such as sexual activity and smoking. In a case-cohort study in Sweden, addition of cyclic progestins was found to counteract the adverse effects of menopausal estrogens on endometrial cancer risk, but the risk of breast cancer remained elevated among combination estrogen-progestin users. A case-control study of trophoblastic diseases in China found that use of oral contraceptives was associated with the risk of complex moles but not with invasive moles.

An association, suggested in an earlier study, between renal pelvis cancer and acetaminophen-containing analgesics is being evaluated in a multicenter case-control study of this tumor.

Nutrition: Evidence from international correlations and migrant populations suggests that diet and nutrition are important in cancer etiology, but specific dietary risk factors have not been well established in case-control and cohort studies. The Program continues to test and generate hypotheses in this area.

Using the follow-up of the First National Health and Examination Study (NHANES) cohort, studies were conducted to evaluate the effects of serum cholesterol and height and weight, in collaboration with the Division of Cancer Prevention and Control (DCPC). Men in the lowest cholesterol quintile had nearly twice the risk of those in the highest quintile for cancer incidence and mortality. Among women, a similar relation was seen for cancer mortality, but cancer incidence in the lowest quintile was only 1.2 times that of women in the highest quintile. The inverse cholesterol-cancer relationship in men was present for determinations made 6 or more years before diagnosis of cancer, which suggests that lowered serum cholesterol may not simply result from preclinical disease. Analysis by site revealed inverse associations for cancers of the lung, bladder, pancreas, and cervix. The low levels of cholesterol appeared to be a risk factor mainly for cancer sites related to smoking, a provocative finding that persisted even after adjustment for smoking.

The relationship of anthropometric variables to risk of breast cancer was also examined in this cohort. Women who developed breast cancer were taller and had greater frame size (elbow width) than non-diseased women. However, body size, defined by weight, relative weight, or skin-fold measurements was not associated with increased risk. The positive association of stature and frame size to breast cancer risk suggests that early nutrition may play an etiologic role.

Whenever possible, case-control studies of various cancers incorporated dietary components designed to evaluate specific hypotheses. In Louisiana, a

study showed fruit intake to be protective for lung cancer, while a small study suggested that vegetable and carotenoid intake lowers the risk of mesothelioma. The latter finding is intriguing since mesothelioma is not an epithelial tumor, and ongoing clinical trials of micronutrients (e.g., beta-carotene) in asbestos-exposed workers should evaluate their impact on mesothelioma, as well as on lung cancer. A study in Louisiana suggested that fruit intake and vitamin C were protective for pancreatic cancer, while consumption of pork products contributed to the excess risk observed among Cajun residents. Studies of oral and esophageal cancer suggested a protective effect of fruit intake that extends beyond items containing vitamin C. A study of laryngeal cancer in Texas found an inverse relation to carotenoid-containing vegetables, similar to an earlier study of lung cancer in New Jersey.

Results from a case-control study of fecal mutagens and colorectal cancer showed a decrease in fecapentaene excretion among the cases, compared to controls, that could not be explained by the effects of diagnostic work-up or surgery. Non-fecapentaene mutagenicity was uncommon in the study group, but no large case-control differences were seen. Fecal bile acid and neutral sterol concentrations are being investigated, controlling for fecal blood content, using the stored samples and same methodological approach. Dietary influences on fecal measurements will be examined based on food frequency and diet recall data collected from study subjects.

Using data from the Breast Cancer Detection Demonstration Project (BCDDP), no relationship was found between coffee or methylxanthine consumption, either past or recent, and the risk of breast cancer. A study is ongoing among American women of Asian ancestry to assess what aspects of the Western diet or lifestyle are associated with the increased breast cancer risk in these migrants, and to evaluate whether dietary factors are crucial during childhood and adolescence. A multicenter case-control study of endometrial cancer is underway to assess nutritional factors and the role of obesity, as measured by dietary recall, anthropometry, and biochemical measurements.

Opportunities to study nutritional hypotheses exist in other countries, where several collaborative case-control and intervention studies are underway. In Shandong, China, an area at high stomach cancer risk, elevated risks were associated with intake of salted food and sour pancakes, while protective effects were seen with a number of vegetables, including ones containing vitamin C and ones of the Allium class (e.g., garlic). The protective effects of Allium vegetables were striking, with a 50% or greater reduction in stomach cancer risk among heavy consumers, an intriguing finding in view of recent reports of tumor inhibition among experimental animals administered Allium compounds. In collaboration with DCPC, a nutrition intervention study in Linxian, China, an endemic area for esophageal cancer, is underway to determine specific micronutrients and trace minerals that may reduce the level of risk. Trials involving nearly 34,000 participants in this high-risk area are midway through a 5-year nutrient supplementation program.

In a case-control study of ovarian cancer in Shanghai, where rates for this cancer are increasing, the risk increased with the intake of fat from animal sources, but not with fat from plant sources. After adjustment for socioeconomic status and other risk factors, women in the highest quartile of animal fat consumption had 1.8 times the risk of those in the lowest quartile. Vegetables, legumes, and vitamin C appeared to protect against ovarian cancer.

In a case-control study of in situ cervical cancer in Australia, women in the lowest quartile of carotenoid, vitamin C, or folacin intake had approximately twice the risk of those in the highest quartile, although the trend was significant only for vitamin C. Retinol intake was not predictive of risk. Among the food items, salad vegetables and fruit juices were the most protective. The levels of total carotenoids and beta-carotene in the plasma were both inversely associated with risk, with women in the lowest quartile of beta-carotene having five times the risk of those in the highest quartile.

Genetic susceptibility: In collaboration with laboratory investigators, epidemiologic and clinical observations have resulted in the delineation of familial cancer syndromes and several leads to mechanisms of host susceptibility. In collaboration with the Massachusetts General Hospital and other research groups, the gene for neurofibromatosis (NF-1) was localized to the long arm of chromosome 17, near the gene for the receptor of the nerve growth factor. Interest was extended this year to the study of NF-2, featuring bilateral neuromas and recently mapped to chromosome 22.

The discovery of the dysplastic nevus syndrome has provided a valuable marker of susceptibility to familial and sporadic melanoma, enabling early detection and treatment of this potentially lethal cancer. Studies of high-risk families, in collaboration with the Massachusetts Institute of Technology, have utilized restriction fragment length polymorphism to localize the melanoma gene to chromosome 1p. In cooperation with the Division of Cancer Treatment, cytogenetic studies of melanoma-prone families have revealed a tendency for chromosome breakage. A large study of multiple endocrine neoplasia, type 1 (MEN-1) has confirmed the location of the gene on 11q. In collaboration with British investigators, a relationship was found between the debrisoquine metabolic phenotype and lung cancer risk, with extensive metabolizers having a significantly increased risk.

Studies of the sarcoma-breast cancer syndrome (Li-Fraumeni syndrome) have been extended to 24 families, and show that the constellation of tumors also includes acute leukemia, brain tumors, and adrenocortical carcinoma. Laboratory studies of the cardinal feature, soft tissue sarcoma, have revealed specific non-random chromosomal translocations, and homozygous deletion of the candidate retinoblastoma gene on 13q14 in 3 of 16 sarcoma specimens. A large family with Wilms' tumor in 7 cousins has provided data for exclusion of linkage with chromosome 11p13 and 11p15 probes, raising the possibility that a familial Wilms' tumor gene is located elsewhere. A multinational registry of the polyposis-hepatoblastoma syndrome has been established and has enrolled 5 hepatoblastoma survivors with polyposis coli, as compared with 0.2 cases expected in the U.S. and Western Europe over the past 3 decades. In the family with a constitutional 3;8 chromosomal translocation and renal carcinoma, the breakpoint at 3p14.2 has been found to be frequently deleted in renal cancer cells of sporadic (non-familial) cases examined cytogenetically and with molecular probes, suggesting inactivation or loss of a recessive oncogene in this region. Examination of 198 offspring of Wilms' tumor patients showed that the hereditary fraction of the neoplasm is lower than predicted previously, and that premature delivery is associated with a history of abdominal radiotherapy for Wilms' tumor in the mother.

The Program's repository of cancer-prone families has become of increasing interest to experimentalists involved in the identification of human oncogenes,

and tissue specimens are made available upon request to the extramural community. Two staff members direct the NIH Interinstitute Medical Genetics Program, which expands opportunities for research, training, and medical care in cancer genetics. Continuing analyses of the Five-Center Study of 2,300 survivors of childhood cancer revealed new data on fertility and reproductive outcomes, and potential gonadal toxicity of treatment. There were fewer marriages and fewer first pregnancies among those who married, but no excess of cancer, birth defects or genetic diseases beyond the expected number of heritable neoplasms.

Environmental pollution: Epidemiologic studies utilize relevant environmental measurements to evaluate the effects of pollutants in the general environment. To test the hypothesis raised by previous Program research that environmental arsenical air pollution in the community is related to lung cancer, a case-control study is underway in Shenyang, China, where that country's largest copper smelter is located in the center of a densely populated residential area. The risk of lung cancer from indoor air pollution is also being investigated in Shenyang, with initial data suggesting a rising lung cancer risk associated with longer duration of exposure to coal-burning stoves, which generate high levels of polycyclic hydrocarbons. Exposures to volatiles from high-temperature wok cooking were implicated in the high risk of lung cancer among nonsmoking women in Shanghai. Fumes from rapeseed and soybean oils were mutagenic in the Ames test, with rapeseed oil volatiles the more potent, further suggesting that indoor pollution from cooking oil vapors may contribute to the elevated rates of lung adenocarcinoma among Chinese women. In addition, alpha track and thermoluminescence dosimeters were evaluated for measuring radon daughter products in residential dwellings. To account for seasonal variations, whole year measurements are being carried out. Collaborative studies to evaluate the relation of indoor radon exposures to lung cancer are underway in New Jersey, Missouri, Sweden, and China.

Using data from the national case-control study of bladder cancer, an elevated risk was found to be associated with the intake of tap water from chlorinated sources of surface water, especially among long-term users. A case-control study is underway in Iowa to clarify the effects of water contaminants, with particular attention to chlorination by-products and agricultural chemicals on the risk of bladder, colon, rectum, kidney, pancreas, and brain cancers. An expanded study of bladder cancer will evaluate risk among population subgroups, such as smokers and nonsmokers.

Infectious agents: Advances in laboratory techniques, such as viral isolation and molecular detection approaches, have opened new avenues for exploring the role of viruses in cancer etiology. Since 1980, a total of five human retroviruses have been discovered, including human T-cell lymphotropic virus type 1 (HTLV-I) which has been linked to a spectrum of T-cell malignancies, and the human immunodeficiency virus (HIV-I) which causes the acquired immunodeficiency syndrome (AIDS). Beginning in 1982, a series of long-range epidemiologic studies has been undertaken by Program staff in several HTLV-I viral-endemic areas. In Jamaica, a case-control study involving 100 incident adult T-cell leukemias (ATL) revealed a 35-fold increased risk among HTLV-I seropositives, a population incidence of 3-5 per 100,000 in the age group at high risk, and an unexpectedly high proportion of cases with HTLV-I antibodies.

Modeling ATL incidence as a function of the number of seropositives suggests that infection at a young age is likely to confer the greatest risk for disease.

In Jamaica, a study of seropositive B-cell chronic lymphocytic leukemia, where the tumor cell immunoglobulin reacted specifically with an HTLV-I antigen, suggested an indirect role of HTLV-I in leukemogenesis. A population-based survey of 14,000 Jamaicans defined a high-risk of HTLV-I seropositivity, with a persistent female predominance from young adulthood. Heterosexual transmission was supported by a link between HTLV-I seropositivity and the number of lifetime sexual partners in a study in Panama; by an association with a positive serologic test for syphilis in Barbados; and by a relation to markers of sexual promiscuity in women, or to prostitute contact and ulcerative genital lesions in men, based on a study of Jamaicans attending a clinic for sexually transmitted diseases. Homosexual contact was also implicated in Trinidad by a sixfold excess risk associated with a promiscuous lifestyle, although HIV was found to be much more readily transmitted. Coinfection with HTLV-I and HIV in this group conferred a significantly higher risk of AIDS development compared to HIV infection alone.

A major commitment to investigate the epidemic of AIDS began in 1981, and continues today. A series of five cohorts, followed since the earliest phase of the epidemic, has provided a data base for understanding the natural history of HIV and its pleiotropic effects. Among seropositive individuals, the risk of AIDS has approached 50% after 6 years of follow-up, with no significant cofactors identified among a variety of lifestyle variables. However, HLA-Dr-1 appears associated with an increased risk for progression to AIDS. A multicenter hemophiliac cohort has allowed more precise quantification of predictors of AIDS risk, particularly a decline in T4 lymphocyte count, appearance of HIV antigen, and increased levels of acid-labile alpha-interferon. This decline in immunity is also associated with increased viremia and heightened infectivity of female spouses, and thus represents a major risk factor for sexual transmission of HIV.

Evaluation of Surveillance, Epidemiology and End Results (SEER) data shows that single young men in San Francisco are at risk not only for Kaposi's sarcoma (KS), but also for tumors related to DNA viruses, notably B-cell lymphomas associated with the Epstein-Barr virus, and hepatoma associated with hepatitis-B. A similar pattern has been seen in surveys of the New York State Cancer Registry. The decline in KS since 1986 and the disproportionate occurrence of KS among the high-risk group of homosexual men suggest that its etiology is linked to a sexually transmitted agent. KS is a current focus of studies in the U.S. and overseas employing newly developed growth factor approaches, and the causes of other AIDS-associated tumors are also under study.

Studies are ongoing to clarify the role of hepatitis-B infection in liver cancer. An earlier cohort study of American veterans, who received contaminated yellow fever vaccine in 1942, revealed a persistence of hepatitis-B markers 43 years after infection, but little or no heightened risk for hepatoma. Case-control studies of liver cancer are underway in the veterans

population to clarify the role of hepatitis-B. Attention is also being directed to Red Cross blood donors, with preliminary evaluation suggesting an excess risk of hepatoma among hepatitis-B carriers.

Preliminary results from a case-control study in Latin America showed that human papillomaviruses (HPV) types 16 or 18 were important risk factors for invasive cervical cancer, although the association was of lesser magnitude than hypothesized on the basis of laboratory findings. The relationship of HPV infections with risk of cervical dysplasia was demonstrated in a Washington, D.C. study, with some evidence that smoking may act synergistically with the virus. Methodological studies revealed that some caution must be exercised in interpreting results of HPV-DNA hybridization assays, particularly since there was considerable variation in typing even when the "gold standard" Southern blot assay was utilized.

Biochemical epidemiology: The power of epidemiologic studies may be increased by incorporating laboratory methods, so-called biochemical or molecular epidemiology. The analyses of biological samples in the laboratory may permit or enhance the study of exposure to oncogenic viruses, dietary components, and environmental pollutants. In addition to measurements of past and current exposures, experimental approaches provide insights to preneoplastic events, host factors, and mechanisms of carcinogenesis.

Among the epidemiologic studies with biochemical components are investigations to detect and quantify in vivo exposures to particular viral and chemical carcinogens or their metabolites, and to newly developed markers of genetic predisposition. Collaboration is ongoing with the DCE Laboratory of Human Carcinogenesis to investigate environmental and genetic aspects of lung and colorectal cancer, and with the Laboratories of Tumor Cell Biology and Tumor Virus Biology in studies of retroviruses and papillomaviruses in human cancer. During the year, biospecimens were collected from a number of epidemiologic studies to measure the influence of human leukocyte antigens (HLA), micronutrients and trace metals, endogenous hormones, metabolic enzymes, mutagenic substances, DNA-carcinogen adducts, and oncogene expression.

Biostatistics: Continued emphasis was given to the development of basic and applied statistical methodology with applications to epidemiology and carcinogenesis research. New avenues of statistical research were initiated to help in evaluating the natural history of AIDS and in assessing the reproducibility of laboratory tests for detecting antibodies to HIV. Estimates of the minimum size of the AIDS epidemic were published, indicating that over five times as many cases as seen to date will eventually be diagnosed, even if no new HIV exposures occur.

Improved methods for finding confidence intervals for the relative difference were developed from previous observations on the ratio of proportions. Homogeneity score tests, which are adjusted for estimation of nuisance parameters, have been developed. Further statistical methods for the testing of genetic models in HLA data and the estimation of the associated parameters have been devised and evaluated. In addition, simplified formulae were derived for estimating sample size requirements for detecting linear trends and for assessing differences in relative risk associated with continuous vs. binary exposure variables. The effects of cluster sampling in telephone surveys, a community-used approach in case-control studies, continued to be examined. The

within-cluster correlations appeared to have minor influences on the variances of the risk estimates for most variables. Other research evaluated stratified vs. pair-matched analyses for discrete variables, the effects of pooling across strata on bias and efficiency, estimation with multiply-matched controls, comparisons between different control series, and characteristics of the case-cohort design.

Published during the year was a monograph dedicated to manuscripts from a conference co-sponsored by the Program on time-related aspects of human carcinogenesis. Two staff members evaluated the statistical issues of carcinogenicity testing for a volume published by the International Agency for Research on Cancer. A monograph dealing with statistical and epidemiologic issues relating smoking and occupation was also published. The Program continued to be responsible for statistical support and consultation to intramural scientists throughout the Institute, ranging from basic laboratory research to community activities in cancer control. With the expansion of applied prevention programs in DCPC, efforts were made to share epidemiologic resources and conduct collaborative projects, particularly in the area of diet and nutrition, and in the utilization of the SEER program for a wide variety of descriptive and analytical studies of cancer etiology and prevention.

Collaborative Activities

Interagency programs: Collaborative studies with other Federal agencies continued to receive high priority to: (1) evaluate urgent issues on which epidemiology has a bearing, including those of immediate regulatory or public policy concern; and (2) stimulate the epidemiologic application of technical and data resources established by the Government for other purposes. Although many research and regulatory agencies are concerned with environmental causes of cancer, few have epidemiologic expertise and require assistance and support on many issues. At this time of fiscal constraint, it is important to increase initiatives to develop and coordinate national data resources that, with proper safeguards, may be tapped for epidemiologic research. An example of such a resource is the Nuclear Regulatory Commission's registry of radiation workers, which can be used to investigate the effects of exposure to ionizing radiation. During the year a staff member was an active advisor on the management of the National Death Index (NDI), located at the National Center for Health Statistics (NCHS). A pilot study was initiated to explore the cost and feasibility of extending the NDI retroactively to cover a significant period before 1979, when coverage now begins.

Exploratory studies are also underway to utilize data on occupational exposure and cancer mortality from several agencies, including the Social Security Administration (SSA), the Internal Revenue Service (IRS), the Bureau of the Census, and NCHS. Collaboration with the National Institute for Occupational Safety and Health (NIOSH) and with NCHS continued in an effort to develop a national reporting system for occupational mortality on the basis of state coding of death certificate entries of usual industry and occupation. Staff members provided advice on modifying the Internal Revenue Code in order to increase opportunities for epidemiologic studies of occupational groups, to broaden access to the IRS address file, and to explore ways to exchange data and ease limitations on the research uses of individually identifiable records. The change in the IRS agreement with NIOSH under which current addresses are furnished to investigators involved in occupational studies, a change that

freed SSA to furnish NCI staff with Social Security numbers needed for the IRS search, proved valuable to NCI staff seeking current addresses of study subjects. Methodological studies evaluated the utility of the one-percent Continuous Work History Sample (CWHS) of the Social Security Administration (SSA) in screening industry-of-employment cohorts for evidence of differential cancer mortality. Other studies were concerned with the feasibility and usefulness of adding to the CWHS file information on specific occupations obtained from the IRS Form 1040, and with the agreement between death certificate information on usual industry of employment and occupation and parallel information obtained by SSA and IRA.

Research using Veterans Administration diagnostic indices of discharge increased during the year, together with research on record-linkage systems utilizing population-based cancer registries. This year, several investigations involved the participation of colleagues from other agencies, including the Centers for Disease Control, NIOSH, Department of Energy, Environmental Protection Agency (EPA), National Oceanic and Atmospheric Administration, Department of Agriculture, and National Research Council.

International projects: Binational programs offer major epidemiologic opportunities for international study, and this year continued emphasis was given to joint studies and exchange programs in several countries. In collaboration with Chinese scientists, case-control studies of cancers of the esophagus, lung, stomach, and ovary, and trophoblastic neoplasia and childhood leukemia were completed in high-risk areas of China. Additional research was initiated in China to follow-up large cohorts of workers exposed to radon, arsenic, silica, and benzene, and to explore risk factors for penile cancer. The risk of thyroid nodules and cancer is being evaluated among Chinese women living in areas of high background radiation in Guangdong province. A cohort study of cancer risk among diagnostic x-ray workers in China was completed. In Italy, a collaborative case-control study of stomach cancer is underway to identify causes of the high rates in certain northern and central parts of that country. Several studies are being conducted in Denmark and Sweden to evaluate the role of radiation, occupational factors, and various medications (e.g., hormones and anticonvulsant drugs) in cancer etiology. In Israel, studies of cancer risk following radiation exposures for ringworm of the scalp, cardiac catheterization, and infertility treatment have continued. In addition to a collaborative research program with scientists at the Radiation Effects Research Foundation in Hiroshima, staff members were also active in the U.S.-Japan program, with emphasis on workshops. One meeting dealt with the marked differences in melanoma occurrence in the two countries and another with the familial syndrome of sarcomas and breast cancer. Two staff members served as foreign co-organizers of the annual international symposium sponsored by the Princess Takamatsu Cancer Research Foundation. This year's subject was "Rare Events as Clues to Cancer Etiology." Meetings were also held to stimulate collaboration under the U.S.-Soviet program, and staff members advised on surveys of Soviet citizens exposed to fallout from the Chernobyl disaster. In several areas, including the Caribbean basin, Latin America, Asia, and Africa, studies are continuing to evaluate the role of retroviruses in human cancer. A new initiative to monitor AIDS-related cancers in Africa is being developed in collaboration with the International Agency for Research on Cancer. Several staff also contributed to workshops and reports sponsored by international agencies, such as the World Health Organization, the International Union Against Cancer, the International Commission on Radiological Protection, and

the International Labor Office. Guest investigators from many countries visited the Program for varying periods of collaborative research.

Other activities: Within the Program, further steps were taken to improve the coordination of epidemiology and biostatistics components, and to stimulate multidisciplinary activities linking epidemiologists with experimentalists. Through the mechanisms of the SEER program, cancer centers, prepaid health plans, and other resources, staff members became further involved in coordinating case-control and other analytical studies with extramural investigators. In addition, several staff were involved with the preparation of comprehensive and critical reviews on a wide variety of topics. Service on interagency and other committees dealing with urgent public health and public policy issues was commonplace. Staff members served on an Office of Science Technology and Policy (OSTP) committee concerned with radiation research and policy coordination; chaired an interagency committee that oversees studies of the health effects of Agent Orange; served on committees of the National Council on Radiation Protection and Measurements dealing with the effects of indoor radon, the potential hazards to astronauts from space radiation, the prenatal effects of ionizing radiation, and the comparative carcinogenicity of radiation and chemicals; and on the advisory committees of the EPA and the National Academy of Sciences dealing with the issue of indoor radon. Staff also contributed to departmental and interagency committees concerned with such issues as AIDS, asbestos, formaldehyde, Agent Orange, pesticides, water pollution, passive smoking, smokeless tobacco, and ultraviolet radiation in relation to possible depletion of the ozone layer.

Although each group in the Program has its own specific mission and objectives, there is a great amount of interaction between the intramural Branches, and several working groups have been formed to help ensure coordination of activities. These groups are concerned, for example, with the development and utilization of epidemiology data resources and record-linkage systems, studies of cancer-prone families, diet and nutrition, female cancers, epidemiologic methods, specimen repositories, and emergent issues (e.g., AIDS). In-house committees continue to scrutinize and evaluate protocols and questionnaires for all intramural projects. These committees have functioned well and have served to strengthen the intramural program by helping to ensure projects of the highest quality. In the aftermath of the formaldehyde study, which raised procedural questions, staff members developed guidelines to formalize mechanisms for undertaking and reviewing occupational studies of a complex and sensitive nature.

Extramural Programs

The Extramural Programs Branch plans and manages a national extramural program of basic and applied research in cancer epidemiology, biostatistics, genetics, and related multidisciplinary activities. The Branch mainly utilizes the grant mechanism, but contracts and cooperative agreements are also employed when appropriate. The Branch consists of program areas in biometry (including genetics), epidemiology, and special emphasis areas of AIDS-related epidemiology and biochemical epidemiology. Staff members keep abreast of scientific developments to identify specific areas of epidemiologic research that need special attention and support.

This year, several initiatives were continued to further stimulate and reorient investigations on the epidemic of AIDS and AIDS-associated neoplasia, utilizing grants and cooperative agreements, plus a contract-based study to investigate the natural history of AIDS in collaboration with the National Institute of Allergy and Infectious Diseases. The biological specimens from this large-scale multicenter collaborative study will be important to clarify the relationships between HIV, immunologic abnormalities, and AIDS. The Branch is also supporting investigations of anogenital cancers, which occur excessively in homosexual populations and have appeared to parallel the epidemic of AIDS. A planning workshop was held with epidemiologists and basic scientists concerning the apparent increased incidence of certain tumors in AIDS patients. A request for applications (RFA) has been issued which focuses on epidemiologic studies of HIV-associated malignancies, and several grant awards will be made. Consideration is being given to revising this RFA in the coming year in an attempt to fund additional studies in this high-priority area.

The Branch attempts to facilitate multidisciplinary research in cancer etiology. In this regard, it reissued an RFA in the area of biochemical epidemiology to stimulate the development, validation and application of laboratory procedures to detect environmental exposures that may affect cancer risk. The cooperative agreements resulting from the initial issuance of the RFA have been jointly supported by NIOSH, EPA, and the National Institute of Environmental Health Sciences. Awardees met again this year with representatives of the Federal organizations to discuss research progress and ways in which cooperative efforts can be made most effective.

A workshop involving NIH staff and extramural epidemiologists was held to review existing mechanisms for extramural support of epidemiologic research. The recommendations were endorsed by the Division of Cancer Etiology Board of Scientific Counselors. As a result of one recommendation, a Small Grants Program for epidemiology and biostatistics was created. Awards are intended to support initiatives that focus on (1) planning of a complex epidemiologic investigation, (2) developing or validating a laboratory procedure for the ultimate purpose of applying it to cancer epidemiologic research, or (3) coordinating an epidemiologic research project for which rapid funding is justified. Other recommendations contained in the report are being pursued and, if implemented, should enhance opportunities for research in the extramural epidemiology community.

The Branch continues to support the congressionally mandated Small Business Innovation Research Program designed to stimulate small business participation in Federal research and development projects. The Branch has worked closely with intramural staff to develop a series of project statements for activities suitable for small business efforts in epidemiology, biostatistics, and related areas.

Prospects

It is difficult to project activities over time, given uncertainties in positions and funding, and in the direction that new findings and opportunities may lead. Nevertheless, we are continuing to strive for a comprehensive, flexible, and balanced research program that will enhance our capacity at the national level to generate fresh ideas and help settle seminal questions in

cancer epidemiology and biostatistics. Emphasis is being given to in-depth analytical studies to identify etiologic agents and elucidate mechanisms of carcinogenesis. Continued efforts are made to utilize, in an efficient and effective manner, resources of the NCI and other Federal agencies.

Staff members continue to provide biometric and epidemiologic support to various parts of the National Cancer Program, to foster parallel and complementary efforts, and to promote epidemiology training opportunities at NIH and elsewhere. The Program is constantly challenged to increase the scope of its extramural and cooperative research and to help develop Institute and Federal programs and policy in all areas related to cancer epidemiology, including etiology and prevention.

After a period of substantial growth over the past decade, the size of the intramural epidemiology program has stabilized. Yet, there remains a need to maintain a capability to analyze descriptive data on cancer statistics, such as those provided by the SEER program and the NCHS (e.g., for development of the cancer maps), to generate and formulate etiologic leads to cancer. It is clear that the major emphasis of the Program should be on analytical epidemiologic studies to pursue etiologic clues, and to identify the lifestyle and other environmental and host factors that pose carcinogenic risks in humans. If new funds and personnel should become available, additional priority would be given to research designed to clarify the role of nutritional factors and general environmental (e.g., air and water) pollutants in cancer etiology, with attention to the development of more precise and innovative ways of measuring exposures. In assessing risk factors, greater emphasis will be given to epidemiologic studies that incorporate biochemical and molecular probes of exposure, response, and mechanisms of action. Studies of cancer-prone families provide exceptional opportunities to apply new molecular techniques, including those related to expression of human oncogenes and genetic-environmental interactions. The AIDS epidemic and associated neoplasia and the study of T-cell leukemia will continue to receive intensive study by linking epidemiology with immunologic and virologic probes, especially those related to retroviruses. The relation of human papillomaviruses to cervical and other cancers will also be emphasized.

Although traditional methods of epidemiology have succeeded over the years in identifying and characterizing many risk factors for cancer, the task ahead appears more formidable as etiologic hypotheses become increasingly specific and complex. With the development of experimental probes, their application in biochemical and molecular epidemiology represents a strategy that will help clarify key issues in cancer etiology.

With the recent updates of the cancer maps and secular trends, further emphasis will be given to understanding reasons for geographic, temporal, and ethnic variations in cancer risk. Attention will also be given to the study of less common neoplasms, involving collaborative case-control studies in several areas or centers, often utilizing the network of SEER registries. Whenever possible, data from epidemiologic studies will be used for methodologic evaluation and development, for investigation of carcinogenic mechanisms of action, and for research into quantitative risk assessment. The staff will continue to provide epidemiologic and biostatistical support to a wide variety of groups involved in efforts to understand and control cancer. The effectiveness of intramural and extramural initiatives will depend upon our

success in promoting interaction and coordination with the other segments of the National Cancer Program. Special efforts will be made to interact more closely with DCPC staff to enhance the flow of ideas from etiologic research to intervention studies, in concerted efforts to develop preventive measures and reduce the toll of cancer as quickly as possible.

ANNUAL REPORT OF

THE BIOSTATISTICS BRANCH
EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1987 through September 30, 1988

The major functions of the Biostatistics Branch are to conduct independent and collaborative investigations, using biometric approaches, into the distribution and determinants of cancer in individuals and populations; to develop and evaluate statistical methods for the design, conduct, and analysis of epidemiologic, experimental and clinical studies of cancer; to conduct basic research in mathematical statistics related to various aspects of cancer; to explore mathematical models to clarify processes of cancer biology and carcinogenesis; to provide statistical consultation to NCI intramural scientists and other groups concerned with cancer research; and to plan and conduct research and developmental work to improve methodology in the application of computers and data processing techniques for cancer research and related programs.

The work of the Biostatistics Branch is accomplished through in-house studies and collaborative projects involving other investigators in this country and abroad. Following is a brief summary of the program as it has evolved and developed during the year. Activities are listed according to section, although often members of several sections are involved in individual projects.

Mathematical Statistics and Applied Mathematics

Activities of the Mathematical Statistics and Applied Mathematics Section are principally concerned with research in statistical methods useful in cancer research and collaboration in the conduct of cancer studies with other branches and laboratories both within and outside the Division of Cancer Etiology (DCE).

Research continued on development of a general score theory of statistical analyses for measures of association in single and stratified 2x2 tables. One paper described modification of homogeneity score tests for situations involving nuisance parameters. It was also shown how score theory can be employed in finding very accurate confidence intervals for the relative difference, a traditional measure of the effectiveness of two treatments. The method is simpler and less computer intensive than the previously proposed method based on the bootstrap method. Another related recent finding is that similarly derived intervals for the difference in proportions are quite accurate without the need to correct for skewness.

Research on small sample logistic models derived exact and approximate tests for comparing hospital and neighborhood controls in doubly-matched case-control studies. Staff are also investigating the derivation of more highly accurate sample size formulas for stratified logistic models of 2x2 tables.

Work continued on developing appropriate models for analyzing HLA studies. One publication showed that Hardy-Weinberg models with no recessive genes and a positive inbreeding coefficient can be indistinguishable from a similar model

with zero inbreeding but with a recessive gene hidden in the apparent homozygotes. Another concerned the bias correction to Bernstein's estimator in generalized ABO-like systems, such as HLA, with further investigation of the efficiency of several bias-corrected non-iterative estimators of the recessive gene frequency. Other research in statistical genetics concerns the comparison of coefficients of linkage disequilibrium in case-control studies. Methods for identifying the Gm haploytypes present in a population on the basis of Gm allotype data were explored, as were possible improvements in score tests for homogeneity of recombination fractions in linkage analysis.

Research continued on methods for analyzing survival curves produced by in vitro exposure of cultured cell lines to DNA-damaging agents, and on statistical methods for identifying "hot spots" for mutation formation in plasmid transfection experiments.

Essentially completed was the development of efficient computer methods for obtaining exact results in the analysis of combined 2x2 tables. Utilizing network theory developed by Mehta and first approximations incorporating bias and skewness corrections developed by Gart, an algorithm has been developed that is more than two orders of magnitude faster than the previous method developed in this section. Further improvements are obtained when two or more tables have equal marginal totals, such as in multiply-matched case-control studies.

Consultation continued in mathematical statistics and collaboration with investigators both in and outside the Division of Cancer Etiology. This included statistical collaboration on studies of fecal mutagenicity and colorectal cancer, time trends in solar ultraviolet (UV) radiation exposure and skin cancer, risk of cancer among aircraft maintenance workers, immunoglobulin types and nasopharyngeal cancer, accutane as an inhibitor of skin cancer in patients with xeroderma pigmentosum, breast cancer screening among young women, cisplatin in the treatment of testicular cancer, genetic markers for obesity, radiation-induced cancer in experimental animals, and chromosome damage and effects of DNA-damaging agents in cultured cells.

Epidemiologic Methods

The Epidemiologic Methods Section conducts research to develop, adapt, and evaluate methodologic procedures useful in epidemiologic studies of cancer. Emphasis is placed on statistical and operational methods for the design, implementation, interpretation and analysis of a broad range of human studies, including both observational and experimental designs.

Work continues on the design and analysis of case-control studies. In collaboration with staff at the National Institute of Child Health and Human Development (NICHD), Branch staff have studied the effects of cluster sampling of controls on standard methods of case-control analysis and have proposed alternative analytical methods. Such cluster samples could arise, for example, in telephone surveys of controls. Pooling across strata in perfectly balanced cohort and case-control studies was shown to lead to tests with size above or below nominal levels and to biased estimates of exposure effect, depending on the generalized linear model considered. Sample size calculations were published for case-control studies with continuous exposures. A paper appeared that described the use of case-control designs in elucidating time relationships between exposure and risk of disease.

One staff member collaborated with staff in the Division of Cancer Prevention and Control (DCPC) to organize a workshop on the impact of errors in measurements of the reliability of epidemiologic studies. Branch members have served as editor and reviewers of papers presented at this conference, which are to be published together.

Work is in progress on projecting cancer risk for individuals with specific risk factors and for populations. A risk model for projecting individualized breast cancer risk was developed in collaboration with staff in DCPC. Risk projections for low-dose radiation exposure have been developed in conjunction with the Committee on the Biological Effects of Ionizing Radiations (BEIR IV) of the National Academy of Sciences (NAS). Methods to investigate and describe the effects of joint exposures have been published in two manuscripts, which investigate the risk of lung cancer in those exposed to radon and other risk factors. A paper has been submitted on variance calculations for risk projections from cohort data. These methods, which have been applied to projecting the risk of recurrence following resection of lung cancer, allow one to assess the uncertainties associated with random error and systematic model misspecification. Two manuscripts have been submitted on the problem of calculating confidence intervals for attributable risks based on logistic modelling of exposures and confounders.

Staff members worked on aspects of the design and analysis of occupational cohort studies. One paper reviewed standard methods of analysis for occupational cohort studies. Another paper described methods for indirect correction for confounding in studies in which data on an important confounder, like smoking status, are not available on individual subjects. Indirect corrections for the excess risk and the excess relative risk were given, in addition to known corrections for the relative risk. Two manuscripts, written in collaboration with Professor Siemiatycki of McGill University, give empirical evidence that reliable inference on occupational exposure is often obtained even in the absence of data on potential confounders. A paper describing the calculation of externally standardized mortality ratios and their variances for data derived from a case-cohort study has been published. Work has been submitted for publication on alternative variance calculations for analyzing and designing economical case-cohort studies.

Detailed statistical methods on "back calculation" for projecting the size of the acquired immunodeficiency syndrome (AIDS) epidemic are to be published. These calculations require neither assumptions on seroprevalence of human immunodeficiency virus (HIV) infection nor on the proportion of seropositives who will develop AIDS and provide a useful complement to projections based on simple extrapolation. Biases that result when conventional analyses of factors thought to modify the risk of AIDS are applied to prevalent cohorts of HIV-seropositive individuals whose dates of seroconversion are unknown have been described in two publications in joint work with Professor R. Brookmeyer of Johns Hopkins University. In collaboration with staff of the Radiation Epidemiology Branch, a compartmental model has been developed to evaluate the effects of screening for HIV and other interventions to retard the epidemic. Other areas of active methodologic research and development include computer programs for epidemiologic analysis with the IBM-PC, methods for sequential monitoring of clinical trials, methods for testing for treatment effect in randomized trials, methods for testing whether a treatment is good for some subsets of patients and harmful to others, and methods for comparing diagnostic tests.

Collaboration within the Epidemiology and Biostatistics Program was extensive. Section staff were involved in a reassessment of thyroid cancer risk in six cohorts exposed to low doses of ionizing radiation. Risks from solar UV radiation were also examined. A paper appeared describing secular trends in UV radiation at eight monitoring locations. Collaboration continued to quantify risks of early menopause following radiotherapy and/or chemotherapy for cancer. Included in AIDS research was a cohort study of high-risk mothers and infants, a cohort study of hemophiliacs, and a study of risk of infection for laboratory workers. Section members also participated in the design and analysis of several studies of cancer in China (see Analytical Studies).

Collaboration with groups outside DCE also continued during the year. One Section member made a major contribution to the report of the BEIR IV Committee of the NAS. One member serves as Chairman of the Operations Committee that monitors the progress of a placebo controlled clinical trial of azidothymidine, sponsored by the Veterans Administration, among patients with AIDS-related complex. In collaboration with the staff at the University of California at Los Angeles (UCLA), one member has written three papers to describe the interactive effects of joint exposures to carcinogens in rodent assays. One member published two papers on the cancer risk of occupational exposure to petroleum derivatives in collaboration with McGill University. One member works on cancer clinical trials at the University of Paris. Models for projecting risk for breast cancer for women with several known risk factors have been refined with collaborators in DCPC. Consultation has also continued with DCPC staff on the design of large-scale interventions to reduce smoking.

Analytical Studies

The Analytical Studies Section conducts investigations to generate and evaluate hypotheses regarding the causes of cancer in human populations. Members of this and other sections of the Branch often work collaboratively with scientists in other institutions in the United States and abroad to gather and analyze epidemiologic data to assess environmental and host determinants of cancer.

Analyses of cancer incidence and mortality: Evaluations of the variation in cancer rates over space and time can often provide leads to etiologic factors.

Trends through the mid-1980s in both incidence and mortality of various cancers, in five areas covered by the Third National Cancer Survey and the SEER program, were described during the year. Noteworthy were the steep rises in the rates of melanoma and multiple myeloma, the rise and fall of endometrial cancer incidence, and the gradual abatement of declines in both stomach and uterine cervix cancers. No evidence of rising rates of cervical cancer has yet been detected, as might have been expected from the rising prevalence of sexually-related risk factors. Concern has arisen of a possible forthcoming epidemic in skin cancer due to a depletion of atmospheric ozone, since marked declines in ozone were documented in Antartica. Branch study, however, found no upward trends in ground-level UV radiation over a 12-year solar cycle period beginning in the 1970s. Thus, rising skin cancer incidence seems not attributable to recent increases in the amount of solar radiation reaching the earth's surface.

Collaborative case-control and cohort studies in the United States: The Branch undertakes collaborative analytical investigations to identify and quantify risk factors for cancer. In the largest investigation of oral and pharyngeal cancer yet conducted, section staff have worked with scientists in Atlanta, New Jersey, Los Angeles, and the San Francisco area in the design and conduct of a population-based case-control study. Analyses of the resultant interview data from nearly 1,200 cancer patients and 1,300 controls, showed smoking and drinking to be the dominant risk factors. The large study size enabled the first clear demonstration of effects of alcohol consumption among lifelong nonsmokers and indicated that smoking and drinking tended to combine more in a multiplicative than additive fashion in affecting oral cancer risk. Risks of oral/pharyngeal cancer were shown to fall sharply following cessation of smoking. Smokeless tobacco was also implicated as a risk factor among nonsmokers, although the numbers of users were too small for detailed analyses of the relative influences of snuff vs. chewing tobacco. Analyses on risks of oral cancer associated with diet have showed significantly lower risks associated with high fruit intake, with those in the highest quartile of consumption at less than half the risk of those in the lowest.

Tobacco and alcohol were also found to be the principal determinants of esophageal cancer in coastal South Carolina, where rates of this tumor have long been elevated among blacks. In this case-control study conducted with the Medical University of South Carolina, consumption of local moonshine whiskies, reported by nearly 90% of the black male patients interviewed, appears to be responsible, at least in part, for the clustering. Higher risks were independently associated with poor nutrition, providing further evidence of a dietary component in the etiology of esophageal cancer and additional clues to its higher rates among blacks than whites. Interviewing continued during the year for another case-control investigation of esophageal cancer. Nearly 600 patients and more than twice as many population-based controls in Atlanta, Detroit, and New York will be enrolled in this collaborative study focusing on differences in exposures and risks between blacks and whites. Utilizing the same control series for comparison, patients with cancer of the pancreas and multiple myeloma are also being enrolled. Each of these cancers occurs more frequently in blacks than whites for as yet unknown reasons.

Analyses of data from a case-control study of laryngeal cancer in coastal Texas were completed. Study subjects were 183 white male cases and 250 frequency-matched controls, relatively large numbers for this uncommon cancer. Cigarette smoking was the strongest risk factor, but excess risks of laryngeal cancer were also linked to alcohol, reduced vegetable intake, and with certain occupations (i.e., construction and metal fabrication).

Field work continued in case-control studies of biliary tract cancer in collaboration with the University of Southern California (USC) and renal pelvis cancer in collaboration with USC, the New Jersey Department of Health, and the University of Iowa. The latter investigation was prompted by an earlier Branch study in Minnesota, which revealed an association between renal pelvis cancer and long-term use of acetaminophin-containing analgesics. The finding was based on small numbers of observations, but is of concern because of a recent report of carcinogenicity in an animal experiment with this commonly used medication. Review this year of data from the Minnesota study found that use of diuretics was associated with increased renal adenocarcinoma risk, consistent with a similar finding from Los Angeles published last year. The biliary cancer study is one of the few etiologic investigations of this relatively rare tumor.

Data analyses continued on two large population-based case-control studies: the national bladder and skin cancer surveys. Both surveys were conducted in the late 1970s, but provide data from nearly 19,000 interviews on population exposures and risk factors for these tumors that are still applicable today. These data provide for the most definitive evaluation of the relation of cigarette smoking to bladder cancer risk. Clear trends were observed with duration and intensity of smoking, with detection, for the first time, of a rapid reduction in risk within a few years of quitting smoking. This pattern was seen both in the U.S. and in Italy, where case-control data also showed markedly higher bladder cancer risk associated with smoking black compared to blond tobaccos. The increased carcinogenic potential of the black tobacco is further suggested by the detection of hemoglobin adducts to 4-aminobiphenyl (a bladder carcinogen) in the blood of smokers of black tobacco.

Cohort analyses to investigate dietary factors in cancer risk are being conducted in collaboration with the University of Minnesota, utilizing data from the Lutheran Brotherhood Study. The cohort consists of 17,818 males who were covered by a Minnesota-based insurance company and who responded to a dietary questionnaire administered during 1966-1967. Work this year extended the mortality follow-up through 1984. Indices for intake of fiber, folate, and several nutrients have been created, and analyses of risks for several cancers (stomach, pancreas, colon/rectum) are continuing.

The Branch has a major role in the National Mortality Followback Survey (NMFS) in collaboration with the National Center for Health Statistics (NCHS). The survey involves the administration of a mail questionnaire to the next-of-kin of 20,000 decedents or about 1% of the deaths occurring in the U.S. in 1986. Among other issues, the survey will evaluate risk factors such as diet, use of tobacco, alcohol and hormones, disease history, and occupation and their relationship to several rare cancers, including male breast cancer, small intestinal cancer, liver cancer among young women, oral cancer among young men, and cancer of the thymus, adrenal, and pituitary glands. NCHS has oversampled 1985 and 1986 deaths to ensure enough deaths from these rare tumors.

Collaborative methodologic studies on various aspects of the mail questionnaire study design have been completed as part of the pretest for the NMFS.

International studies: A major emphasis is the conduct of analytical biometric/epidemiologic studies in areas of the world that offer special opportunities for research on cancer etiology. The Branch is collaborating with the Chinese Academy of Medical Sciences and other governmental institutions in five case-control studies in high-risk areas of China. These include investigations of esophageal cancer in Linxian, with the world's highest rates of this cancer; stomach cancer in Shandong Province, where salt consumption is high and where certain foods are regularly eaten that are uncommon elsewhere in China; choriocarcinoma in Beijing; and lung cancer in Shanghai and in Shenyang, to evaluate reasons for the high rates of lung tumors in Chinese women. The Shenyang study will also examine the role of arsenical air pollution from China's largest nonferrous smelter, extending earlier Branch studies in the U.S. suggesting a link between this exposure and lung cancer. In total, over 9,000 interviews are being conducted in these investigations.

Reports published during the year from the Shanghai study show that smoking is the dominant cause of lung cancer in men and a risk factor for both squamous cell carcinoma and adenocarcinoma in women. The findings seem likely to dispel the notion that Chinese cigarettes are not harmful. Most female patients were nonsmokers, however, so other factors account for their high rates. What these factors are remain to be clarified, but a clue arises from the observations of increased risk among women reporting greater frequencies of high temperature wok cooking, increased house smokiness and eye irritation when cooking, and greater use of rapeseed cooking oils. The link to rapeseed oil is intriguing since rapeseed volatiles have been reported to be mutagenic in the Ames test. Prior infection with tuberculosis (TB) was also associated with lung cancer in both sexes. The association was strongest for persons with TB diagnosed 5-20 years prior to lung cancer, after the widespread use of chemotherapeutic agents, although no evidence was found to incriminate isoniazid (INH), the most widely used anti-TB drug, and suggests that long-term survivors of TB face an increased risk of lung cancer. Occupational analyses revealed a lowered risk of lung cancer among workers in the cotton textile industry, a major employer in Shanghai. The finding is consistent with reports from the U.S., and raises the possibility of exposure to protective agents (e.g., endotoxins) in the work environment.

In Shandong, dietary differences distinguished cases and controls. The stomach cancer patients preferred and consumed more salted foods and more of the local favorite sour pancakes, and significantly less fresh vegetables. The most marked protective effects were for vegetables of the allium class, particularly garlic, of note because of the tumor-inhibitory properties of allium reported from experimental studies. In the Linxian case-control study, consumption during adulthood of pickled vegetables was not found to be the strong risk factor it was suspected to be. Intake of pickled vegetables in either the 1950s or 1970s was not higher among the esophageal cancer patients, nor was intake of fresh fruit and vegetables lower. Instead the cases were characterized by lower fluid and higher wheat and corn intake, similar to Iran where clusters of high esophageal cancer rates have also been found. Assays of nitrosamines in urine specimens collected in Linxian from preclinical esophageal cancer patients, persons with esophageal dysplasia, and normal controls were initiated during the year in collaboration with the DCE Laboratory of Comparative Carcinogenesis, NCI, to assess whether N-nitroso compounds may be involved in the cancer or its primary precursor lesion. Increases in cell proliferation, based on tritiated thymidine labelling assays performed at the Memorial Sloan-Kettering Cancer Center, were found among Linxian residents with histologic evidence of dysplasia.

A large-scale randomized intervention trial continued in Linxian during the year. One component of the trial focuses on 3,400 persons with esophageal dysplasia. Another involves 30,000 villagers from the general high-risk population. Participants have been randomly assigned to one of several groups to receive different combinations of vitamins and minerals or placebo over a 5-year period. A two-group design (multivitamin vs. placebo) is being used for the dysplasia trial. A more complicated eight-group design, based on a one-half replicate of a 2^4 factorial design, is used for the general population trial. A brief questionnaire was administered and 5 ml serum obtained from each participant prior to enrollment. The studies, now in their third and second years, respectively, will evaluate whether certain groups of vitamins and

minerals can inhibit late-stage progression to cancer in a high-risk population with multiple micronutrient deficiencies, and may have considerable implications for the effectiveness of nutritional intervention programs in lowering cancer incidence worldwide.

Additional collaborative research in China was conducted during the year, including cohort studies evaluating the cancer experience of occupational groups exposed to (1) benzene, (2) silica, and (3) radon and arsenic. The benzene study will enroll over 100,000 workers and enable the most precise estimation yet available of the benzene-leukemia dose-response relation, plus an evaluation of whether benzene induces other cancers. The silica study will assemble between 5,000-10,000 persons in central China with silicosis, plus 30,000 persons heavily exposed to silica without silicosis, for evaluation of this agent that has been recently shown to initiate and promote cancer in experimental animals. The radon/arsenic study focuses on nearly 30,000 tin miners and smelter workers in Yunnan province, where lung cancer rates are exceptionally high, and will assess interactions between these carcinogens and examine time-related factors in cancer induction.

A case-control study of stomach cancer, in collaboration with the Center for the Study of Cancer in Florence and other Italian institutions, was conducted to investigate reasons for the high risk of this cancer in north and central parts of Italy. Some provinces in this region have among the highest stomach cancer mortality rates in the world, approaching or exceeding those in Japan. Branch staff have collaborated in the design and conduct of the study which is concentrating on dietary exposures, including the apparently high consumption of preserved meats in the high-risk areas. Interviewing of cancers patients and 800 controls was completed during the year, with data analyses about to begin.

Ongoing collaboration with investigators in Sweden on the analysis of linked census and cancer registry data has evaluated occupational factors in the occurrence of several neoplasms. This large national resource, linking data from the 1960 census with cancer incidence data covering the entire Swedish population over the period 1961-1979, is being utilized to generate and test hypotheses regarding occupation and cancer. Recently an increased risk of male breast cancer has been found in workers employed in the formulation of estrogenic creams, and an elevated risk of malignant melanoma has been uncovered among printers exposed to unrefined lubricating oils. Other analyses have identified new occupational leads for bladder cancer, multiple myeloma, and leukemia.

Information Resources Management

The Branch is responsible for assuring adequate computer-related support to the epidemiologists and biometricians throughout the Epidemiology and Biostatistics Program. The major recurring activities of the Information Resources Management Section continue to include responsibility for coordinating all contract-related activities pertaining to support services acquisition, administration and monitoring the computer support contracts for the Epidemiology and Biostatistics Program and assignment of computer analysts to support individual research projects. Support ranges from routine data analysis operations to research and development activities associated with the development of highly specialized systems designed for sophisticated data analysis. Significant activities included the implementation of a Biospecimen Inventory System that has stand-

ardized the protocol for collecting, storing and disseminating biospecimen materials; the development and release for use of a generalized analytical package which calculates the number of expected events in a study group based on the rate of events in some standard or referent population; the design of a quality assurance/quality control program to manage the growing inventory of software products, data bases and other resource files used throughout the Program; the evaluation of a new computer hardware/software configuration as an alternative computing resource for Program investigators; and the analysis of local area network requirements for the new consolidated office building.

SUMMARY REPORT

BIOSTATISTICS BRANCH

PROGRESS ON RESEARCH CONTRACTS

The Branch's research contracts (FY-88 expenditures $1,100,00) support unique or rare opportunities to study populations with unusual risk patterns and exposures in order to understand better the etiology of certain cancers.

To evaluate risk factors in high cancer rate areas and in heavily exposed populations in China, collaborative contracts have been negotiated with the Chinese Academy of Medical Sciences (CAMS), the Liaoning Province Public Health Station, and the Chinese Academy of Preventive Medicine (CAPM). One (CP-21012) supports four case-control studies: esophageal cancer in Linxian, where esophageal cancer rates are the highest in the world; lung cancer in Shanghai, where rates are exceptionally high in women even though few smoke; choriocarcinoma in Beijing; and stomach cancer in Shandong province, where unusual opportunities exist to evaluate dietary factors. Interviewing of cancer patients and controls was completed last year with collaborative data analyses continuing this year. A second contract (CP-41019) enables the conduct of a 5-year randomized intervention trial in Linxian to test whether vitamin/mineral supplementation can lower the incidence of this tumor. Over 33,000 persons are enrolled and monitoring of their cancer experience continues. A third CAMS contract (CP-71118) funds studies of silica- and radon/arsenic-exposed workers and of penis cancer, with study procedures pilot tested during the year. The investigation (CP-51021) in Sheyang, one of China's most heavily polluted cities, continued interviewing of lung cancer cases and population controls. Contract CP-71119 with the CAPM supports a cohort survey evaluating risks from benzene among approximately 100,000 workers in 12 cities. Air monitoring data from factories were obtained during the year and used to classify workers according to benzene exposure.

A multicenter study of stomach cancer is ongoing in collaboration with the Preventive Oncology Center of Florence, Italy (CP-51019). Enrolling cases and controls and interviewing and biologic specimen collection in two high-risk (Firenze, Forli) and two low-risk (Genova, Cagliari) areas continued during the year in order to determine dietary and other contributors to the substantial variation in gastric cancer in Italy.

Finally, the NCI and other components of the Public Health Service are collaborating with the National Center for Health Statistics in a survey involving interviews with the next-of-kin of over 20,000 persons who died in 1986 (CP-60500). Included are decedents of rare cancers (e.g., tumors of the small intestine, endocrine glands other than thyroid, liver among young women and oral cavity among young men) for which a large national survey is needed to assemble sufficient numbers of cases for analysis of environmental risk factors.

BIOSTATISTICS BRANCH

RESEARCH CONTRACTS ACTIVE DURING FY-88

Institution/Principal Investigator Contract Number	Title
Chinese Academy of Medical Sciences Dr. Li Bing NO1-CP-21012	Collaborative Epidemiologic Cancer Research in China
Chinese Academy of Medical Sciences Dr. Li Bing NO1-CP-41019	Nutrition Intervention Trial in Linxian China
Liaoning Public Health and Anti-epidemic Station Dr. Xu Zhao-Yi NO1-CP-51021	An Epidemiologic Study of Lung Cancer and Air Pollution in Shenyang, China
Centro Per Lo Studio E la Prevenzione Oncologica Dr. Eva Buiatti NO1-CP-51019	Case-control Study of Stomach Cancer in Italy
National Center for Health Statistics Mr. Sam Seeman YO1-CP-60500	National Mortality Follow-back Survey
Chinese Academy of Medical Sciences Dr. Li Jun Yao NO1-CP-71118	Epidemiologic Studies of Cancer in China
Chinese Academy of Preventive Medicine Dr. Yin Songnian NO1-CP-71119	An Epidemiologic Study of Benzene Exposure in China

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04265-23 BB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Consulting in Statistics and Applied Mathematics

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J. J. Gart	Chief, MSAMS	BB	NCI
Others:	R. E. Tarone	Mathematical Statistician	BB	NCI
	H. M. Pettigrew	Mathematician	BB	NCI
	D. G. Thomas	Mathematical Statistician	BB	NCI
	J. Nam	Mathematical Statistician	BB	NCI
	A. M. Smith	Statistician (Health)	BB	NCI

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Biostatistics Branch

SECTION

Mathematical Statistics and Applied Mathematics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	3.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

It is the purpose of this study to collaborate with NCI researchers on mathematical problems related to many areas of cancer research. Consulting assistance in statistical methodology and applied mathematics is provided for NCI investigators and to some extent for NCI contractors. In general, the study is devoted to accelerating the use of quantitative methodology in various aspects of the NCI intramural and extramural programs.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

J. J. Gart	Chief, MSAMS	BB	NCI
R. E. Tarone	Mathematical Statistician	BB	NCI
H. M. Pettigrew	Mathematician	BB	NCI
D. G. Thomas	Mathematical Statistician	BB	NCI
J. Nam	Mathematical Statistician	BB	NCI
A. M. Smith	Statistician (Health)	BB	NCI

Objectives:

The principal objectives are (1) to collaborate with NCI scientists on mathematical problems related to cancer research, (2) to provide consulting assistance in statistics and applied mathematics to NCI investigators, and (3) to accelerate the use of quantitative methodology in various aspects of the NCI intramural program and extramural program.

Methods Employed:

The methodology of applied mathematics, mathematical statistics and probability is applied to biomedical problems. Often various variations of existing techniques are developed to suit the special requirements of a particular problem.

Major Findings:

During this year, the staff advised and collaborated with many investigators in the major divisions of research in the National Cancer Institute, as well as some contractors and investigators elsewhere. The various projects are grouped below in terms of the divisions and areas of the projects.

Division of Cancer Etiology - Epidemiology and Biostatistics Program

Dr. Pettigrew continues his collaboration with Dr. Mark Schiffman of the Environmental Epidemiology Branch in projects involving fecal mutagenicity and colorectal cancer. He is a co-author of two papers that are being prepared reporting some of the results.

Dr. Tarone is advising Mr. Scotto of the Biostatistics Branch on the use of time series methods to assess the significance of time trends in ultraviolet exposure.

Mr. Nam also collaborates with Mr. Scotto on the seasonality of non-melanoma skin cancer in a special cancer survey. Dr. Tarone is collaborating with Dr. McLaughlin of the Biostatistics Branch on an international case-control study of renal cancer.

Dr. Pettigrew has been collaborating with Dr. Robert Spirtas in the analysis of data from a retrospective mortality study of aircraft maintenance workers in Utah and has assisted in the revision of a paper of which he is a co-author.

Dr. Tarone continues to collaborate with Dr. Paul Levine of the Environmental Epidemiology Branch on a study of Gm and Km immunoglobulin allotypes in nasopharyngeal cancer patients from Malaysia.

Dr. Tarone continues to advise members of the Clinical Epidemiology Branch on statistical issues in the analysis of age-adjusted mortality and incidence rates.

Division of Cancer Etiology - Other Programs

Dr. Pettigrew has continued to provide advice and assistance to Dr. James L. Murray of the Radiation Effects Branch on the project investigating late effects of protracted irradiation on dogs being carried out at Argonne National Laboratory under NCI contract.

Dr. Pettigrew is also advising Dr. Raymond Gantt of the Radiation Effects Branch on the results of an NCI review of pathology specimens from an experiment conducted by the Food and Drug Administration to study the relative effectiveness of ^{131}I and X-rays in producing thyroid cancer in rats.

Dr. Tarone is providing statistical assistance to Dr. Paul Donovan of the Laboratory of Comparative Carcinogenesis in studies performed to estimate in vivo mutation rates in mouse fetuses.

Dr. Tarone continues to collaborate with Dr. Katherine Sanford of the Laboratory of Cellular and Molecular Biology on experiments to elucidate the mechanisms of increased susceptibility to chromosome damage in cultured cells from patients with cancer-prone disorders. He continued collaboration with Dr. Sanford and Dr. Michael Potter of the Laboratory of Genetics (Division of Cancer Biology and Diagnosis) to investigate the association in mice between susceptibility to plasmacytomagenesis and enhanced chromatid radiosensitivity.

Dr. Pettigrew will be assisting Dr. Carl E. Smith of the Chemical and Physical Carcinogenesis Branch to review data collected under NCI contracts by the late Dr. Albert Segaloff of the Alton Ochsner Clinic.

Dr. Tarone completed collaboration with Dr. Kenneth Kraemer of the Laboratory of Molecular Carcinogenesis and Dr. Gary Peck of the Dermatology Branch (Division of Cancer Biology and Diagnosis) in a study of the efficiency of accutane as an inhibitor of skin carcinomas in patients with xeroderma pigmentosum. He is collaborating with Dr. Kraemer and Susanna Barrett of the Dermatology Branch in a study to identify a DNA repair defect in cultured cells from Cockayne syndrome patients by measuring their capacity to repair UV-irradiated plasmids.

Division of Cancer Prevention and Control

Dr. Tarone is collaborating with Dr. Charles Smart and Dr. Kenneth Chu of the Early Detection Branch in a reevaluation of breast cancer mortality in the Health Insurance Program clinical trial of screening using mammography. Dr. Tarone continues to advise Dr. Donald Henson of the Early Detection Branch on various statistical applications.

Division of Cancer Biology and Diagnosis

Dr. Tarone continues his collaboration with Dr. Jay Robbins and others in the Dermatology Branch in experiments to study the in vitro sensitivity of cultured cells from patients with cancer-prone diseases or with primary neuronal degenerations after exposure to DNA-damaging agents. His collaboration with Dr. Robbins and scientists at the Harvard University Laboratory of Radiobiology on the effects of DNA-damaging agents on in vitro cell survival also continues.

Dr. Tarone advised Dr. Robert Moses of the Immunology Branch regarding statistical methods for assessing the impact of quantitative co-variables on mortality using censored survival data.

Division of Cancer Treatment

Dr. Tarone continued to provide statistical assistance to Dr. Eddie Reed of the Clinical Oncology Program in studies of patients treated with cisplatin for testicular cancer. He assisted in preparation of a manuscript reporting a direct association between prognosis and the level of cisplatin adducts formed in peripheral blood from testicular cancer patients.

Other Parts of NIH

Mr. Nam and Dr. Gart have collaborated with Dr. Richard Fabsitz of the Epidemiology and Biometry Program of National Heart, Lung, and Blood Institute on possible genetic markers for obesity from HLA (human leukocyte antigen) data from the Framingham Heart Study. A significant positive association of obesity with AW30 is found in both males and females.

Other Activities

Mr. Thomas placed in service the section's first advanced microcomputer system and is in the process of converting existing software and developing new software for it. He is also assisting in the training of other section members in its use. Mr. Thomas has selected several similar systems with appropriate software (including statistical typing software) as cost effective tools to further the research and consulting efforts of the section. These systems will facilitate the sharing of software, developed in this section, that we continue to provide to other researchers throughout the world.

Publications:

Chu KC, Brown CC, Tarone RE, Tan WY. Differentiating among proposed mechanisms for tumor promotion in mouse skin with the use of the multievent model for cancer. JNCI 1987;79:789-96.

Chu KC, Smart CR, Tarone RE. Analysis of breast cancer mortality and stage distribution by age for the HIP clinical trial. JNCI (In Press)

Ganges MB, Tarone RE, Jiang H, Hauser C, Robbins JH. Radiosensitive Down syndrome lymphoblastoid lines have normal ionizing-radiation-induced inhibition of DNA synthesis. Mutation Res (In Press)

Gart JJ, Krewski D, Lee PN, Tarone RE, Wahrendorf J. Statistical methods in cancer research, Vol. III. The design and analysis of long-term animal experiments. IARC Sci Publ 1986;79:219.

Kraemer KH, DiGiovanna JJ, Moshell AN, Tarone RE, Peck GL. Prevention of skin cancer in xeroderma pigmetosum with the use of oral isotretinoin. N Engl J Med (In Press)

Levine PH, Blattner WA, Clark J, Tarone R, Maloney B, Murphy EM, Gallo RC, Robert-Guroff M, Saxinger WC. HTLV-I geographic distribution and identification of a new high-risk population. Int J Cancer (In Press)

Nove J, Tarone RE, Little JB, Robbins JH. Radiation sensitivity of fibroblast strains from patients with Usher's syndrome, Duchenne muscular dystrophy, and Huntington's disease. Mutation Res 1987;184:29-38.

Potter M, Sanford KK, Parshad R, Tarone RE, Price FM, Mock B, Huppi K. Genes on chromosomes 1 and 4 in the mouse are associated with repair of radiation-induced chromatin damage. Genomics (In Press)

Reed E, Ozols RF, Tarone RE, Yuspa SH, Poirier MC. Platinum-DNA adducts in nucleated peripheral blood cell DNA correlate with disease response in ovarian cancer patients receiving platinum-based chemotherapy. Proc Natl Acad Sci USA 1987;84:5024-8.

Sanford KK, Parshad R, Greene MH, Tarone RE, Tucker MA, Jones GM. Hypersensitivity to G2 chromatid radiation damage in familial dysplastic nevus syndrome. Lancet 1987;2:1111-6.

Seguin L, Tarone RE, Liao K, Robbins JH. Ultraviolet light-induced chromosomal aberrations in cultured cells from Cockayne syndrome and complementation group C xeroderma pigmentosum patients. Am J Hum Genet 1988;42:468-75.

Tarone RE, Liao K, Robbins JH. Effects of DNA-damaging agents on Down syndrome cells. Implications for defective DNA-repair mechanisms. In McCoy EE, Epstein CJ, eds. Oncology and immunology of Down syndrome. New York: Alan R Liss, 1987;93-113.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04267-23 BB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Research in Mathematical Statistics and Applied Mathematics

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	J. J. Gart	Chief, MSAMS	BB NCI
Others:	R. E. Tarone	Mathematical Statistician	BB NCI
	H. M. Pettigrew	Mathematician	BB NCI
	D. G. Thomas	Mathematical Statistician	BB NCI
	J. Nam	Mathematical Statistician	BB NCI
	A. M. Smith	Statistician (Health)	BB NCI

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Biostatistics Branch

SECTION

Mathematical Statistics and Applied Mathematics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	3.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

It is the purpose of this project to conduct research in mathematical statistics, probability, and applied mathematics, and especially to develop new statistical methodology which is applicable to the biomedical sciences. Particular subjects of interest are the methodology of analyzing survival curves and proportions, and statistical methods in cancer epidemiology and statistical genetics, such as the analyses of the relative risk and human leukocyte antigen (HLA) data.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

J. J. Gart	Chief, MSAMS	BB	NCI
R. E. Tarone	Mathematical Statistician	BB	NCI
H. M. Pettigrew	Mathematician	BB	NCI
D. G. Thomas	Mathematical Statistician	BB	NCI
J. Nam	Mathematical Statistician	BB	NCI
A. M. Smith	Statistician (Health)	BB	NCI

Objectives:

To conduct research in mathematical statistics, probability, and applied mathematics; to develop new statistical methodology which is especially appropriate to biomedical sciences.

Methods Employed:

The methods employed are the modern theories of mathematical statistics, probability, and applied mathematics. High speed electronic computers are often used to compute appropriate mathematical tables, to test approximations by simulation techniques, and to do exact permutational analyses.

Major Findings:

The research of the members of this section covers a wide spectrum of topics in mathematical statistics, probability, and applied mathematics. These are summarized below.

John J. Gart has continued his development of a general score theory of statistical analyses for measures of association in single and stratified 2x2 tables. The latest work, done with Jun-mo Nam, shows how this theory can be employed in finding very accurate confidence intervals for the relative difference, a traditional measure of the effectiveness of two treatments. The method is simpler and less computer intensive than the previously proposed method based on the bootstrap method. Another related recent finding is that similarly derived intervals for the difference in proportions are quite accurate without the need to correct for skewness. Other work on a small sample logistic model is the derivation of exact and approximate tests for comparing hospital and neighborhood controls in doubly-matched case-control studies. John J. Gart, with Jun-mo Nam is also investigating the derivation of more highly accurate sample size formulas for stratified logistic models of 2x2 tables. John J. Gart and Jun-mo Nam are continuing their joint work on appropriate models for analyzing HLA studies. Their most recent work resulted in a publication showing that Hardy-Weinberg models with no recessive genes and a positive inbreeding

coefficient can be indistinguishable from a similar model with zero inbreeding but with a recessive gene hidden in the apparent homozygotes.

Robert E. Tarone completed work on a paper describing modification of homogeneity score tests for situations involving nuisance parameters, and continues research on the theory of score tests, particularly with regard to small sample power. He continues research on methods for analyzing survival curves produced by in vitro exposure of cultured cell lines to DNA-damaging agents, and is investigating statistical methods for identifying "hot spots" for mutation formation in plasmid transfection experiments. Robert Tarone continues to investigate methods for identifying the Gm haploytypes present in a population on the basis of Gm allotype data, and is also investigating possible improvements in score tests for homogeneity of recombination fractions in linkage analysis.

Jun-mo Nam has completed and published his research on the bias correction to Bernstein's estimator in generalized ABO-like systems, such as HLA. He goes on to investigate the efficiency of several bias corrected non-iterative estimators of the recessive gene frequency. Other research in statistical genetics concerns the comparison of coefficients of linkage disequilibrium in case-control studies. Other problems in statistical methodology being addressed are the optimum allocation of sample sizes in stratified case-control studies when cost per individual may vary by case or control and over strata, finding confidence intervals for the median lethal dose (LD50) in quantal bioassays by the score method, comparing cyclic trends in incidence of disease, and evaluating the adequacy of the chi-square goodness of fit test in sparse multinomial data. Also, together with John J. Gart, Jun-mo Nam is studying the bias correction for the unconditional maximum likelihood estimator of the common slope in stratified analyses of logistic models.

Hugh M. Pettigrew is continuing his research in the areas of risk assessment, synergism, and time-related factors in epidemiology, and in studying problems in the analysis of log-normal data, such as that arising from occupational exposures. His interest in tumor growth kinetics and the mathematical theory of epidemics continues.

Donald G. Thomas has essentially completed the development of efficient computer methods for obtaining exact results in the analysis of combined 2x2 tables. Utilizing network theory developed by Mehta and first approximations incorporating bias and skewness corrections developed by Gart, an algorithm has been developed that is more than two orders of magnitude faster than the previous method developed in this section. Further improvements are obtained when two or more tables have equal marginal totals, such as in multiply-matched case-control studies. A paper detailing these techniques explicitly for microcomputers is being prepared for publication. Alroy M. Smith provides computer support on several of these research projects.

Publications

Gart JJ. The equivalence of two corrections to the approximate mean of an entry in a contingency table. Biometrika 1987;74:661-3.

Gart JJ, Nam J. Approximate interval estimation of the ratio of binomial parameters: A review and corrections for skewness. Biometrics 1988;44:323-38.

Gart JJ, Nam J. The equivalence of two tests and models for HLA data with no observed double blanks. Biometrics (In Press)

Nam J. Bias correction for Bernstein's estimator in generalized ABO-like systems. Proc Tenth Korea Symp Sci Tech: Mathematics and statistics. Seoul: Korean Fed of Sci and Tech Assoc 1987;31-5.

Nam J. A simple approximation for calculating sample sizes for detecting linear trend in proportions. Biometrics 1987;43:701-5.

Nam J, Gart JJ. On two tests of fit for HLA data with no double blanks. Am J Hum Genet 1987;41:70-6.

Tarone RE. Homogeneity score tests with nuisance parameters. Commun Stat [A] (In Press)

Tarone RE. Score statistics. In: Johnson NL, Kotz S, eds. Encyclopedia of statistical sciences, Vol. 8, New York: J Wiley & Sons, 1988;304-8.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04269-17 BB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biomedical Computing - Consultation, Research and Development Service

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	J. Michael Stump	Chief, IRMS	BB NCI
Others:	D. J. Grauman	Computer Systems Analyst	BB NCI
	R. I. Ramsbottom	Computer Specialist	BB NCI
	B. L. Stephenson	Computer Specialist	BB NCI
	R. S. Wolfson	Computer Programmer/Analyst	BB NCI

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Biostatistics Branch

SECTION

Information Resources Management Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
6.0	5.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Information Resources Management Section executes a broad program of computer-related support and services that extends beyond the Epidemiology and Biostatistics Program to other outside institutions and organizations that collaborate in the mission and objectives of the NCI. The Section's mission includes: 1) planning and conducting research and development work to improve methodology in the application of computers and data processing techniques in support of research conducted and coordinated by NCI investigators and their collaborators; 2) serving as the focal point in the Epidemiology and Biostatistics Program for the procurement, management and monitoring of support services contracts, and for the evaluation and procurement of automatic data processing (ADP) and word processing equipment as well as data resources used by staff investigators; 3) providing liaison, consultation and collaboration to NCI investigators on the design, development and operation of data processing and information systems; and 4) representing the Division of Cancer Etiology in providing consultation, guidance and assistance to the National Cancer Institute and the Division of Computer Research and Technology (DCRT) on ADP and office automation issues, problems and operations.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

J. Michael Stump	Chief, IRMS	BB	NCI
Dan J. Grauman	Computer Systems Analyst	BB	NCI
Richard I. Ramsbottom	Computer Specialist	BB	NCI
Boyd L. Stephenson	Computer Specialist	BB	NCI
Ruth S. Wolfson	Computer Programmer/Analyst	BB	NCI

Objectives:

To provide computer-related consultation, liaison and collaboration to NCI investigators and to other Government agencies, private institutions and individual investigators who collaborate with the National Cancer Institute. Emphasis is placed on providing support for the design, development and operation of data management, computer statistical analysis and information and reporting systems for a large program of epidemiological and biostatistical research. Overall coordination is provided for the management of various computer support services obtained under contract, for the procurement of other Epidemiology and Biostatistics (E&B) Program research and resource contracts and for the acquisition and utilization of various information resources and automatic data processing equipment used by staff of the E&B Program. Research and development studies are conducted in order to improve methodology in the application of computers and data processing techniques in support of scientific research conducted by the E&B Program.

Methods Employed:

The Information Resources Management Section (IRMS) continues to execute a broad program of consultation and service in support of research projects having data management and statistical computing requirements. While the primary focus of Section activities is directed towards support of Epidemiology and Biostatistics Program research, IRMS staff have applied technical expertise to projects originating from various investigators throughout the NCI. The major recurring activities of the Section include contract procurement and administration, information management and dissemination, as well as technical and consultative support to E&B Program investigators on research studies.

Major Findings:

The concept of a centralized organization focusing on overall coordination of computer-related activities has become increasingly important as the investigative units of the E&B Program that are supported by the IRMS continue

to mature into full-fledged and specialized programs of research. The continuing growth of study initiatives has resulted in an explosion of data and information gathering, processing, and analysis creating the concomitant need for additional support services. This year, the Section's most noteworthy new initiatives included: 1) the assembling, editing and NCI-wide distribution of a Software and Data Resources Inventory, a compilation of general descriptions of data management and statistical software available to support epidemiologic and biostatistical research; 2) the planning and logistics involved in phasing out an antiquated word processing system and replacing it with new personal computer hardware/software configurations; and 3) assessing the E&B Program's need for a local area network capability.

Individual staff members continued to provide support to a large number of new and ongoing projects. This support has ranged in scope from routine data analysis operations to research and development activities associated with complex data management and sophisticated data analysis. Several projects or activities receiving support included: 1) consulting on the Michigan poly brominated bithenyl study, 2) troubleshooting for personal computer problems, 3) establishing an automated inventory system to keep track of the proliferating personal computers and related hardware/software systems, and 4) designing a system to produce death rates for any selected 4-digit nternational classification of disease code or group of codes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04475-11 BB

PERIOD COVERED

October 1, 1987 through September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Skin Cancer and Solar Radiation Program

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J. Scotto	Health Services Director	BB	NCI
Others:	T. R. Fears	Mathematical Statistician	BB	NCI

COOPERATING UNITS *(if any)* Interfederal Agency Task Force on Ozone Monitoring and Health Effects of Solar Ultraviolet, EPA (H. Pitcher, J. Miller, J. Hoffman); NOAA (G. Cotton, J. De Luisi, L. Machta); NASA (J. Frederick); Temple Univ. (F. Urbach, D. Berger), G.W. Univ. (De Fabo). U., Chicago.

LAB/BRANCH

Biostatistics Branch

SECTION

Analytical Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	1.25	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project provides measurements and statistical analyses of epidemiological, environmental, and photobiologic data relevant to the etiology of skin cancer, including malignant melanoma. Through these studies, NCI provides research in response to Public Law 95-95 (Amendment to the Clean Air Act) and the Federal stratospheric ozone protection policy program. A new international agreement calls for a worldwide limitation and eventual freezing of chlorofluorocarbon production, which has been linked to recent stratospheric ozone depletions. However, anticipated concomitant increases in solar ultraviolet of wavelengths from 290 to 330 nm (ultraviolet) which would cause increases in skin cancer incidence, including melanoma, were not observed in eight geographic areas of the United States from 1974 to 1985. Detailed time series summaries of daily, monthly and annual amounts of UVB from these and other NCI incidence survey locations are being utilized to refine our dose-response estimates, and to provide comparisons with surface and stratospheric measurements of ozone and other meterological factors (e.g., UVB-absorbing aerosols) which may clarify apparent discrepancies in trends. Adjusting for constitutional and environmental factors, we define populations with high risks of skin cancer in areas with varying UVB exposure. New estimates of dose-response according to cell type continue to show that the effect of increases in UVB would be greatest for squamous cell carcinomas, which would be twice as great as those for basal cell carcinomas, and four times as great for skin melanomas. Caucasians in the southern regions of the United States are twice as likely to develop skin cancer and melanoma in their lifetimes as those residing in northern regions. Preliminary studies indicate that a photosensitive, natural element found in human skin may be associated with increased skin cancer risk.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

J. Scotto	Health Services Director	BB NCI
T. R. Fears	Mathematical Statistician	BB NCI

Objectives:

The major objectives of this study are to provide epidemiologic data relative to the etiology of skin cancer, including malignant melanoma and to evaluate the potential human effects of harmful solar ultraviolet radiation (UVB, i.e., wavelengths between 290nm and 320nm). In particular (1) to provide measurements of solar ultraviolet exposure necessary to ascertain the human health effects of ultraviolet (UV) radiation resulting from anticipated ozone depletions in our biosphere; (2) to provide basic data to reduce the degree of uncertainty in dose-response estimators; (3) to provide specific host and environmental data on populations suspected to be at high or low risk of skin malignancy; (4) to provide an estimate of the proportion of skin cancer in the community relative to other cancers; (5) to identify local factors in the community; (7) to provide basic epidemiologic data to elucidate the multifactorial etiology of skin cancer; (8) to estimate trends in skin cancer morbidity and mortality; and (9) to develop dose-response models which may explain initiator/promoter factors associated with UVB radiation exposure.

Methods Employed:

Photobiologic measurements of UVB are obtained at 20 geographic locations throughout the United States. The locations range from coast to coast and include the Hawaiian Islands at 19 degrees north latitude, and Seattle at 47.5 degrees north latitude. At several stations, daily readings have been monitored for an entire solar cycle of 11 years. NCI has been collaborating with National Oceanic and Atmospheric Administration (including its network of weather stations) and Temple University (developers of the Robertson-Berger UVB meter) in obtaining, monitoring, calibrating, and editing ground level readings of solar radiation. The direct measurements obtained from ground level R-B meters are calibrated to count in terms of biological skin erythema, i.e., sunburn on a typical untanned, caucasian skin. The minimal erythema dose (MED) is equivalent to approximately 30 mJ/cm^2. Time series analyses are employed to measure UV-B trends and compare with ozone measurements obtained from domestic and international sources. Also, air pollution measurements (e.g., SO_2, NOx, CO_2) from the Environmental Protection Agency are utilized to study trends of UV-B-absorbing particulates which may account for apparent discrepancies at specific urban sites. Monochromatic estimates of electromagnetic energy within the UV-B waveband which were derived from satellite data are also utilized. Currently, there are a dozen stations where population-based morbidity surveys were conducted for skin cancer or skin melanoma; and seven of these are participating in NCI's continuing Surveillance, Epidemiology, and End Results (SEER) Program. Information on associated constitutional and environmental

factors were obtained by interviewing random samples of skin cancer patients from registry files, and random samples of individuals from households in the general population from telephone exchange numbers (i.e., the random-digit dialing telephone procedure). Analytical methods include newly developed weighted logistics regression techniques and stratified odds-ratio procedures to estimate relative risks and dose-response. Actuarial methods are used to derive lifetime probability estimates.

Census data are used to provide detailed population estimates specific for age, race, sex and geographic location. Also, available population details according to ancestry and ethnicity are utilized to account for Hispanic caucasians, who are known to be at lower risk for skin cancer than Anglo caucasians. Specific analyses considered anatomical sites and histologic types.

Major Findings:

The amount of solar ultraviolet UV-B wavelengths of 290 to 320 nm reading the earth's surface has not increased at eight geographic locations in the United States from 1974 to 1985, a period of about one solar cycle. Overall, an average annual decrease of about 0.7 percent was observed, with 3 of 8 locations showing no statistically significant trends. Similar patterns were noted for 6 other U.S. locations where UVB monitors were in operation for shorter time periods.

Increasing amounts of tropospheric ozone and urban air pollution are suspected as contributing factors which may account for decreasing UVB trends. However, at Mauna Loa, a remote, sparsely populated location situated at 3.4 km above sea level, UV did not increase during the 1980s, in contrast to stratospheric ozone decreases reported during similar time spans. Our research has prompted investigations of the influence of UVB-absorbing particulates in the atmosphere.

Our findings further suggest that lifestyle patterns of sunlight exposure, and not stratospheric ozone depletions, may be primarily responsible for recent increases in skin cancer incidence including melanoma. It is expected, however, that future ozone depletions, which are projected to increase throughout the 21st century, will result in excess risks for skin cancer and other diseases if preventive measures are ignored.

Except for the beneficial photobiologic effects of UVB exposure on the development of vitamin D through the skin, excess amounts of UVB reaching the earth's surface will change our ecology and do much harm to life on our planet. Recent concerns have also focused on the negative correlations of breast cancer and colon cancer mortality rates with sunlight exposure and a deficiency of dietary vitamin D among older men and women. Current studies will explore the UV hypotheses for other diseases not seriously considered by most researchers in the past.

Preliminary analyses of data from a pilot study obtained from collaborators at George Washington University indicate that a photosensitive, natural element found in human skin may be involved in the immunosupression process through the

Langerhans' cells. Adequate photochemical epidemiologic studies are required to substantiate early impressions and findings with respect to skin cancer risk among specific population groups.

In assessing the relationship of UVB exposure and cutaneous malignancies, new analyses with improved statistical methodology indicate that UVB remains the principal component after adjusting for certain host and environmental factors, such as skin and eye color, freckles, common moles or birthmarks, ethnicity, suntan ability, and outdoor occupations. However, the biological amplification factors (BAF), i.e., the relative changes in incidence which may be expected should UVB exposures increase by a certain percentage, may be a bit less than those which we provided from our earlier, unadjusted estimates. But the basic relationship between cell types remains unchanged; namely, that the effect of UVB on squamous cell carcinomas of the skin may be twice as great as that for basal cell carcinomas, and four times as great as that for skin melanomas. The BAFs were also found to be greatest for the exposed anatomical sites. The variances of the new estimates were substantially reduced, thus improving the reliability of the dose-response estimates.

Lifetime probabilities of developing skin cancer and skin melanoma were derived using survival data for specific geographic areas. After adjusting for deaths from other causes, caucasians residing in the southern regions of our country are at greater risk than their counterparts in northern regions, by a factor of about two.

Constitutional and environmental factors associated with increased risk include fair-skin complexion, light eyes or hair color, freckles, and Irish/Scottish ancestry, as well as certain skin conditions requiring medical treatment such as moles, acne, warts, or psoriasis. In addition, individuals who were exposed to radiation (therapy), coal tar/pitch or industrial chemicals were also found to be at higher relative risk than those not having these conditions or exposures.

Factors which were found to be associated with reduced risk include ability to deep tan and not sunburn, Mexican/Spanish ancestry, and indoor workplace or principal occupation. Attributable risk (AR) estimates were calculated to measure the impact of these factors on the population risk for skin cancer. AR's for the positive factors were found to range from 3 to 38 percent; and those for the negative factors were found to range from 4 to 26 percent. UV effects were found to be significant and persistent after adjusting for these associated host and environmental factors.

During the 1970s, incidence rates for skin cancer and melanoma were found to be increasing at annual rates of 3 and 6 percent, respectively. Based on these rates cases would double within the next 15 years. However, during the early 1980s skin melanoma incidence rates leveled off, with decreases observed among caucasian women. This trend did not persist as surveillance and reporting procedures had apparently changed in certain SEER areas during 1984 and 1985, resulting in the highest overall incidence rate for 1985 that has ever been reported in the U.S. Time series methods will be utilized to account for recent short-term interventions in making projections for skin melanoma incidence and mortality by specific geographic area.

Among high risk groups, estimates of relative risk were generally comparable for basal cell carcinoma and squamous cell carcinoma among men and women. Individuals treated for moles or acne, however, appear to be at greater relative risk for BCC (4.0 to 4.4) than for SCC (2.1 to 2.4).

Basal cell and squamous cell carcinoma are usually found on exposed areas of the body (over 80%); but skin melanoma predominate on the trunk (45%) in white males and on the legs (35%) in white females. Dose response patterns according to anatomical site appear to be consistent for nonmelanoma skin cancer, but show evidence of differences of degree of association for skin cancer.

Skin cancer incidence in Kauai, Hawaii indicate that risk among caucasians is the highest found in the United States. Also, incidence rates among Japanese Americans living in Kauai were found to be relatively high. Etiologic factors, i.e., detailed ethnicity and exposure patterns, are being pursued.

Ocular melanoma incidence patterns do not resemble those for other melanomas. However, there is concern that individuals residing at south pole regions may be at excess risk to eye diseases as well as skin malignancies because of the great depletions (40% and more) of stratospheric ozone recently observed in that area. We are collaborating with National Science Foundation programs to investigate this problem.

With respect to noncutaneous melanomas it appears that melanomas of the vagina and genitalia follow eye melanomas in terms of frequency of occurrence among women. Additional studies which include hypotheses of hormonal factors and environmental exposures other than sunlight are indicated. Such studies may also help clarify the influence of chemical and occupational exposures, as well as socioeconomic effects, in the etiology of skin melanoma.

Publications:

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Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum: Cutaneous, ocular, and neurologic abnormalities in 830 published cases. Arch Dermatol 1987;123:241-50.

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Scotto J. Nonmelanoma skin cancer-UVB effects. In: Titus, JG. eds. Effects of changes in stratospheric ozone and global climate: stratospheric ozone. United Nations Environment Program and Environmental Protection Agency. 1986;2:33-61.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04500-11 BB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Methodologic Studies of Epidemiology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	M. Gail	Medical Statistical Investigator	BB NCI
Others:	J. Benichou	Guest Researcher	BB NCI
	W. Blot	Chief	BB NCI
	T. Fears	Mathematical Statistician	BB NCI
	J. Lubin	Health Statistician	BB NCI
	J. McLaughlin	Senior Staff Fellow	BB NCI
	S. Wacholder	Senior Staff Fellow	BB NCI

COOPERATING UNITS *(if any)* Mayo Clinic (S. Wieand), Univ. of Paris (C. Chastang), Cmte. on Biological Effects of Ionizing Radiation of the Natl. Acad. of Sci., Memphis State Univ. (Y. Tan), Chinese Acad. of Med. Sci. (Y. Liu), McGill Univ. (J.F. Boivin, J. Siemiatycki), Johns Hopkins Univ. (R. Brookmeyer, S. Piantadosi)

LAB/BRANCH

Biostatistics Branch

SECTION

Epidemiologic Methods Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	2.1	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A paper has been submitted on new methods for analyzing case-control studies in which controls were selected by cluster sampling. A conference was held on the effects of measurement errors on the reliability of epidemiologic studies, and staff are editing papers from this conference for publication. Methods for projecting cancer risk for individuals and populations were applied to cohorts at high risk for breast cancer and to those exposed to radiation. Variance calculations for such risk projections were derived for cohort data and for attributable risk estimates obtained from logistic models for case-control data. Complex models of the effects of joint exposures were used to study the risks associated with radon exposure. A paper appeared on indirect corrections for confounding in occupational cohort data in which confounder information is not available for individuals. A paper appeared that describes the calculation of standardized mortality ratios and their variances from case-cohort data and methods for assessing the efficiency of the case-cohort design for internal comparisons have been submitted for publication. Sample size calculations were published for case-control designs using logistic regression models with continuous covariates and general relative risk functions. Papers appeared on the effects of pooling data across strata in perfectly balanced cohort and case-control designs and on robust methods of covariate adjustment for testing for treatment effects in randomized clinical trials. Software is being developed to carry out epidemiologic analyses on the personal computer. A manuscript is in press that describes the method of "back calculation" for projecting the size of the acquired immune deficiency syndrome (AIDS) epidemic, and two papers appeared that describe biases in the conventional analysis of prevalent cohort data, such as seropositive persons at risk for AIDS. A compartmental model has been developed to evaluate the effects of potential interventions, like screening for human immunodeficiency virus, on the spread of the epidemic.

Project Description

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

M. Gail	Medical Statistical Investigator	BB	NCI
W. Blot	Chief	BB	NCI
J. Benichou	Guest Researcher	BB	NCI
T. Fears	Mathematical Statistician	BB	NCI
J. Lubin	Health Statistician	BB	NCI
S. Wacholder	Senior Staff Fellow	BB	NCI
J. McLaughlin	Senior Staff Fellow	BB	NCI
S. Bale	Staff Fellow	EEB	NCI
J. Boice	Chief	REB	NCI
L. Brinton	Chief, Environmental Studies Section	EEB	NCI
D. Byar	Chief	BB, DCPC	NCI
S. Green	Medical Researcher	DCPC	NCI
D. Levin	Senior Investigator	DCPC	NCI
J. Mulvihill	Chief, Clinical Genetics Section	CEB	NCI
C. Schairer	Health Statistician	EEB	NCI

Objectives:

To develop, adapt, and evaluate methodologic procedures useful in epidemiologic studies of cancer. Emphasis is placed on statistical and operational methods for the design, implementation, interpretation and analysis of a broad range of human studies, including both observational and experimental designs.

Methods Employed:

A variety of techniques are applied, including the formulation and testing of epidemiologic procedures, such as the use of surrogate controls, the development and use of computer algorithms, and reliance on the methods of biostatistics and mathematical analysis. These methods are applied to data generated by investigators in the Biostatistics Branch and other branches within the Epidemiology and Biostatistics Program, and elsewhere.

Major Findings:

Work continues on methods for selecting controls and other aspects of the design and analysis of case-control studies. In collaboration with the National Institute for Child Health and Human Development (NICHD), branch staff have submitted a paper on the effects of cluster sampling of controls on standard methods of case-control analysis and have proposed alternative analytical methods. Such cluster samples could arise, for example, in telephone surveys of controls. A paper on the effect of pooling across strata in perfectly balanced cohort and case-control studies was published. Such pooling may lead to tests with size above or below nominal levels, and to biased estimates of exposure effect, depending on the generalized linear model considered. One paper

describes sample size calculations for case-control studies with continuous exposures. Another paper describes the role of case-control studies and other designs in elucidating time relationships between exposure and risk of disease.

Detailed statistical methods on "back calculation" for projecting the size of the AIDS epidemic are to be published. These calculations require neither assumptions on seroprevalence of HIV infection nor on the proportion of seropositives who will develop AIDS and provide a useful complement to projections based on simple extrapolation. When conventional analyses of factors thought to modify the risk of AIDS are applied to cohorts of HIV seropositive individuals whose dates of seroconversion are unknown, biases may result. These biases, which are especially serious if the factors are also associated with the date of infection, have been described in two publications in joint work with Professor R. Brookmeyer of the Johns Hopkins University. In collaboration with staff at Radiation Epidemiology Branch, a compartmental model has been developed to evaluate the effects of screening for HIV and other interventions to retard the epidemic.

Work is in progress on projecting cancer risk for individuals with specific risk factors and for populations. A risk model for projecting individualized breast cancer risk was developed in collaboration with staff in (Division of Cancer Prevention and Control). Risk projections for low dose radiation exposure have been developed in conjunction with the Committee on the Biological Effects of Ionizing Radiation. Methods to investigate and describe the effects of joint exposures have been published in two manuscripts, which investigate the risk of lung cancer in those exposed to radon and other risk factors. A paper has been submitted on variance calculations for risk projections from cohort data. These methods, which have been applied to projecting the risk of recurrence following resection of lung cancer, allow one to assess the uncertainties associated with random error and systematic model misspecification. Similar calculations for population-based case-control studies are in progress, and two manuscripts have been submitted on the problem of calculating confidence intervals for attributable risks based on logistic modeling of exposures and confounders.

Two papers appeared on sequential monitoring of clinical trials, and another paper was published on robust hypothesis testing for treatment effects when needed covariates have been omitted from a generalized linear model. A new test to determine whether one treatment is beneficial in some subsets of patients and harmful in others ("qualitative interaction") has been developed in collaboration with Dr. S. Piantadosi of the Johns Hopkins University.

One Branch member continues to collaborate with members of the Radiation Epidemiology Branch to develop an extensive set of programs for epidemiologic analysis with the IBM-PC.

Staff members worked on aspects of the design and analysis of occupational cohort studies. One paper reviewed standard methods of analysis for occupational cohort studies. Another paper described methods for indirect correction for confounding in studies in which data on an important confounder, like smoking status, are not available on individual subjects. Indirect corrections

for the excess risk and the excess relative risk were given, in addition to known corrections for the relative risk. The adequacy of these indirect corrections was shown to depend greatly on the underlying risk model for the joint effects of the exposure and confounder. Two manuscripts, written in collaboration with Professor Siemiatycki of McGill University, give empirical evidence that reliable inference on occupational exposure is often obtained even in the absence of data on potential confounders. A paper has been published describing the calculation of externally standardized mortality ratios and their variances for data derived from a case-cohort study. In collaboration with Professor Boivin of McGill University, one staff member has developed ideas for the investigation of second cancers using cancer registry data. Work has been submitted for publication on alternative variance calculations for pseudo-likelihood estimates of relative risk from the case-cohort design. This design offers potential economies for occupational cohort studies and for other large cohort studies.

Branch members are collaborating with Professor Y. Tan of Memphis University and with Dr. Y. Liu of the Chinese Academy of Medical Sciences to evaluate newly proposed alternatives to logistic regression for the analysis of case-control data. In collaboration with Dr. S. Wieand of the Mayo Clinic, a manuscript has been submitted on methods for comparing diagnostic tests. A paper criticizing newly proposed methods for detecting excess risk in family pedigree studies has appeared. Innovative power calculations for cluster sampling to determine seroprevalence of HTLV-I virus were required to assess the feasibility of a collaborative project with members of the Viral Epidemiology Section of NCI's Environmental Epidemiology Branch.

One staff member collaborated with staff in DCPC to organize a workshop on the impact of errors in measurements on the reliability of epidemiologic studies. The organizers are editing a volume which will contain papers given at this conference.

Publications:

Benichou J, Chastang C. Sequential analysis of randomized clinical trials with a censored response criterion: Use of the triangular test. Th rapie 1987;42:295-9.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04779-12 BB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Field Studies in High Risk Areas

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	W. Blot	Chief	BB	NCI
Others:	J. Fraumeni, Jr.	Associate Director	E&B	NCI
	R. Hoover	Chief	EEB	NCI
	T. Mason	Chief, PSS	EEB	NCI
	B. Stone	Mathematician	BB	NCI

COOPERATING UNITS *(if any)* LA St. Univ. (P. Correa); Univ. TX (P. Buffler); Med. Univ. SC (S. Schuman); NJ Dpt. Health (J. Schoenberg); Chinese Acad. Med. Sci. (B. Li); Shanghai Cancer Inst. (Y. Gao); Center Prev. Med. (E. Buiatti); Univ. So. Ca. (S. Preston-Martin); Emory Univ. (R. Greenberg); CA. Hlth. Dpt. (D. Austin)

LAB/BRANCH

Biostatistics Branch

SECTION

Analytical Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7.5	6.5	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The objectives of this project are to identify and describe environmental and host determinants of cancer in areas at high risk of cancer through the use of analytical epidemiologic and biometric techniques, particularly case-control studies of specific cancers. Completed during the year were case-control studies of esophageal cancer in coastal South Carolina, oral cancer in Atlanta, New Jersey, Los Angeles, and San Francisco, and laryngeal cancer in Texas. Analyses from South Carolina showed that esophageal cancer risk is strongly increased among heavy users of alcohol, especially moonshine, but that low intake of fruits and vegetables also contributes to elevated mortality from this tumor. In the four-center study, smoking and drinking tended to combine in a multiplicative fashion to enhance oral cancer, with heavy consumers experiencing more than 35-times the risk of abstainers. Several international studies are underway to take advantage of unique opportunities to evaluate diet and other factors, including air pollution, in the etiology of cancer. Smoking was shown to be the dominant cause of lung cancer among men in Shanghai, while exposures to cooking oil volatiles were implicated in the high risk of lung adenocarcinoma among women, most of whom were nonsmokers. Consumption of fermented pancakes, a preference for salty food, and smoking were related to the high risk of stomach cancer in Shandong China, while protective effects were found for vegetable intake. A case-control study of gastric cancer continued in areas of Italy that have among the world's highest rates of this malignancy. Also in operation is a randomized intervention trial in Linxian, China, to assess the role of vitamin/mineral supplementation on reducing the area's extraordinarily high cancer risk.

PROJECT DESCRIPTION

Names, Title, Laboratory and Institute Affiliations of Professional Personnel Engaged on this project:

W. Blot	Chief	BB	NCI
J. Fraumeni, Jr.	Associate Director	E&B	NCI
R. Hoover	Chief	EEB	NCI
T. Mason	Chief, PSS	EEB	NCI
B. Stone	Mathematician	BB	NCI
L. Pickle	Health Statistician	EEB	NCI
L. Brinton	Chief, ESS	EEB	NCI
L. Pottern	Epidemiologist	BB	NCI
L. Brown	Epidemiologist	BB	NCI
J. Lubin	Health Statistician	BB	NCI
R. Ziegler	Cancer Expert	EEB	NCI
M. Linet	Cancer Expert	BB	NCI
R. Hayes	Cancer Expert	EEB	NCI
A. Ershow	Senior Staff Fellow	BB	NCI
J. McLaughlin	Senior Staff Fellow	BB	NCI
S. Wacholder	Senior Staff Fellow	BB	NCI
M. Schiffman	Medical Staff Fellow	EEB	NCI
D. Silverman	Epidemiologist	BB	NCI
P. Greenwald	Director	DCPC	NCI
P. Taylor	Epidemiologist	DCPC	NCI
J. Tangrea	Pharmacologist	DCPC	NCI

Objectives:

To identify and describe the environmental determinants of cancer in areas where cancer rates are high.

Methods Employed:

Field studies are conducted in areas of the United States and abroad where cancer rates are high and etiologic hypotheses can be tested. The studies are generally case-control investigations whereby cancer patients and controls, or their next-of-kin in the event they have died, are interviewed regarding lifetime histories of residence, occupation, tobacco consumption, diet, and medical or other factors. Comparison of responses between the cases and controls are made by analytical biometric and epidemiologic techniques to identify, estimate, and evaluate cancer risk factors. When a particular suspect environmental or occupational exposure among a well-defined population group is recognized, cohort investigations may be initiated to determine the group's cancer experience. Often both the case-control interview and the cohort studies are preceded by reviews of appropriate death certificates and medical records for cancer cases and controls for comparisons of available information. Occasionally randomized experimental trials may be initiated to test the effectiveness of suspected protective agents in the high risk areas.

Major Findings:

A large case-control study of oral cancer (1200 cases, 1300 controls) in Atlanta, New Jersey, Los Angeles, and the San Francisco area was completed during the year. Smoking and drinking were shown to be the dominant risk factors. The large study size enabled the first clear demonstration of effects of alcohol consumption among lifelong nonsmokers and indicated that smoking and drinking tended to combine more in a multiplicative than additive fashion in affecting oral cancer risk. Risks of oral/pharyngeal cancer were shown to fall sharply following cessation of smoking. Smokeless tobacco was also implicated as a risk factor among nonsmokers, although the numbers of users were too small for detailed analyses of the relative influences of snuff vs. chewing tobacco. Analyses of risks of oral cancer associated with diet revealed strong protective effects associated with fruit consumption, with one-half the risks among those in the highest compared to lower quartile of intake.

Tobacco and alcohol were also found to be the principal determinants of esophageal cancer in coastal South Carolina, where rates of this tumor have long been elevated among blacks. In this case-control study conducted with the Medical University of South Carolina, consumption of local moonshine whiskey, reported by nearly 90% of the black male patients interviewed, appears to be responsible, at least in part, for the clustering. Higher risks were independently associated with poor nutrition, providing further evidence of a dietary component in the etiology of esophageal cancer and additional clues to its higher rates among blacks than whites. Interviewing continued during the year and will continue through 1988 for another case-control investigation of esophageal cancer. Nearly 600 patients and more than twice as many population-based controls in Atlanta, Detroit, and New York will be enrolled in this collaborative study focusing on differences in exposures and risks between blacks and whites. Utilizing the same control series for comparison, patients with pancreas cancer and multiple myeloma are also being enrolled. Each of these cancers occurs more frequently in blacks than whites for as yet unknown reasons.

Analyses of data from a case-control study of laryngeal cancer in high risk areas of coastal Texas were completed. Study subjects were 183 white male cases and 250 frequency-matched controls, relatively large numbers for this uncommon cancer. Cigarette smoking was the strongest risk factor, but excess risks of laryngeal cancer were also linked to alcohol, reduced vegetable intake, and with certain occupations (i.e., construction and metal fabrication).

Long-term analgesic use was implicated as a risk factor for renal pelvis cancer in an earlier Branch study in Minnesota where kidney cancer risks are high, although the number of involved cases was small. To investigate further, a case-control study of pelvis and ureter cancer was begun last year in collaboration with the New Jersey Department of Health and the Universities of Iowa and Southern California. Interviewing of over 400 cases and an equal number of controls has now been completed.

A major emphasis is the conduct of analytical biometric/epidemiologic studies in areas of the world that offer special opportunities for research on cancer

etiology. The Branch is collaborating with the Chinese Academy of Medical Sciences and other governmental institutions in five case-control studies in high-risk areas of China. These include investigations of esophageal cancer in Linxian, with the world's highest rates of this cancer; stomach cancer in Shandong Province, where salt consumption is high and where certain foods are regularly eaten that are uncommon elsewhere in China; choriocarcinoma in Beijing; and lung cancer in Shanghai and in Shenyang, to evaluate reasons for the high rates of lung tumors in Chinese women. The Shenyang study will also examine the roll of arsenical air pollution from China's largest nonferrous smelter, extending earlier Branch studies in the U.S., suggesting a link between this exposure and lung cancer. In total, over 9,000 interviews are being conducted in these investigations.

Analyses published during the year from the Shanghai study show that smoking is the dominant cause of lung cancer in men and a risk factor for both squamous cell carcinoma and adenocarcinoma in women. The findings seem likely to dispel the notion that Chinese cigarettes are not harmful. Most female patients were nonsmokers, however, so that other factors account for their high rates. What these factors are remain to be clarified, but a clue arises from the observations of increased risk among women reporting greater frequencies of high temperature wok cooking, increased house smokiness and eye irritation when cooking, and greater use of rapeseed cooking oils. The link to rapeseed oil is intriguing since rapeseed volatiles have been reported to be mutagenic in the Ames test. Prior infection with tuberculosis was also associated with lung cancer in both sexes. The association was strongest for persons with tuberculosis diagnosed 5-20 years prior to lung cancer, after the widespread use of chemotherapeutic agents, although no evidence was found to incriminate isoniazid (INH), the most widely used anti-TB drug, and suggests that long-term survivors of TB face an increased risk of lung cancer. Occupational analyses revealed a lowered risk of lung cancer among workers in the cotton textile industry, a major employer in Shanghai. The finding is consistent with reports from the U.S., and raises the possibility of exposure to protective agents (endotoxins) in the work environment. Interviewing of nearly 2400 lung cancer patients and controls was completed during the year in Shenyang, with data analyses now underway.

In Shandong, dietary differences distinguished cases and controls. The stomach cancer patients preferred and consumed more salted foods and more of the local favorite sour pancakes, and significantly less fresh vegetables. The most marked protective effects were for vegetables of the Allium class, particularly garlic, of note because of the tumor inhibitory properties of Allium reported from experimental studies.

In the Linxian case-control study, consumption during adulthood of pickled vegetables was not found to be the strong risk factor it was suspected to be. Intake of pickled vegetables in either the 1950s or 1970s was not higher among the esophageal cancer patients, nor was intake of vegetables lower. Instead the cases were characterized by lower fluid and higher wheat and corn intake, similar to Iran where clusters of high esophageal cancer rates have also been found. Assays of nitrosamines in urine specimens collected in Linxian from

preclinical esophageal cancer patients, persons with esophageal dysplasia, and normal controls continued during the year in collaboration with the Laboratory of Comparative Carcinogenesis, NCI, to assess whether N-nitroso compounds may be involved in the cancer or its primary precursor lesion. Increases in cell proliferation, based on tritiated thymidine labelling assays performed at the Memorial Sloan-Kettering Cancer Center, were found, however, among Linxian residents with histologic evidence of dysplasia.

A large-scale randomized intervention trial continued in Linxian during the year. One component of the trial focuses on 3,000 persons with esophageal dysplasia. Another involves 30,000 villagers from the general high-risk population. Participants have been randomly assigned to one of several groups to receive different combinations of vitamins and minerals or placebo over a 5-year period. A two group design (multivitamin vs. placebo) is being used for the dysplasia trial. A more complicated eight group design, based on a one-half replicate of a 2^4 factorial design, is used for the general population trial. A brief questionnaire was administered and 5 ml serum obtained from each participant prior to enrollment. The studies, now in their third and second years, respectively, will evaluate whether certain groups of vitamins and minerals can inhibit late stage progression to cancer in a high-risk population with multiple micronutrient deficiencies, and may have considerable implications for the effectiveness of nutritional intervention programs in lowering cancer incidence worldwide.

Additional collaborative research in China was conducted during the year, including cohort studies evaluating the cancer experience of occupational groups exposed to (1) benzene, (2) silica, and (3) radon and arsenic. The benzene study will enroll over 100,000 workers and enable the most precise estimation yet available of the benzene-leukemia dose-response relation, plus an evaluation of whether benzene induces other cancers. The silica study will assemble between 5,000-10,000 persons in central China with silicosis, plus 30,000 heavily exposed to silica without silicosis, for evaluation of this agent has been shown to initiate and promote cancer in experimental ani a . The radon/arsenic study focuses on nearly 30,000 tin miners and smelter workers in Yunnan province, where lung cancer rates are exceptionally high and will assess interactions between these carcinogens and examine time-related factors in cancer induction.

A case-control study of stomach cancer, in collaboration with the Center for the Study of Cancer in Florence and other Italian institutions, was conducted to investigate reasons for the high risk of this cancer in parts of north central Italy. Some provinces in this region have among the highest stomach cancer mortality rates in the world, approaching or exceeding those in Japan. Branch staff have collaborated in the design and conduct of the study which is concentrating on dietary exposures, including the apparently high consumption of preserved meats in the high-risk areas. Interviewing of cancers patients and controls was computed during the year, with data analyses on information from over 1600 subjects about to begin.

Continuing during the year was a multicenter study in Latin American to investigate reasons for the high rates of invasive cervical cancer. Interviews with women will focus on sexual history, reproductive factors, contraceptive behavior, medical history, and diet. Husbands of women who report only one sexual partner will be interviewed in order to evaluate the role of a "male factor" in the etiology of cervical neoplasia. (See also Z01CP04501-10 EEB.)

Publications:

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You WC, Blot WJ, Cheng YS, Ershow A, Yang ZT, An Q, Henderson B, Xu GW, Fraumeni JF Jr, Wang TG. Diet and the high risk of stomach cancer in Shandong China. Cancer Res (In Press)

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CONTRACTS IN SUPPORT OF THIS PROJECT:

WESTAT, INC. (N01-CP-31041-01)

Title: Support Services for a Case-Control Study of Oral and Pharyngeal Cancer

Current Annual Level: Funding completed in FY85

Man Years: 16

Objective: To provide technical, managerial, and computer support for an epidemiologic study of oral and pharyngeal cancer in four areas of the United States.

Major Contributions: Study development, forms design and data collection were completed. Data coding, keying, editing and statistical analyses are in progress.

WESTAT, INC. (N01-CP-01044)

Title: Support Services for Epidemiologic Studies

Current Annual Level: $2,200,000 (total for all support services, including services in addition to those in high risk areas of the U.S.)

Man Years: 45

Objective: To provide technical, managerial, and computer support for epidemiologic studies of cancer, including those in high risk areas.

Major Contributions: Interviewing and/or computational support was conducted for studies of esophageal cancer in South Carolina. Forms design, field survey management training and data processing were provided for case-control studies of cancers of the lung, stomach, and esophagus and for the cohort and intervention trials in China.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05498-03 BB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Consulting on Epidemiologic Methods

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	M. Gail	Chief, Epidemiologic Methods Section	BB NCI
Others:	T. Fears	Mathematical Statistician	BB NCI
	J. Lubin	Health Statistician	BB NCI
	J. Benichou	Guest Researcher	BB NCI
	S. Wacholder	Senior Staff Fellow	BB NCI

COOPERATING UNITS *(if any)* Lung Cancer Study Group, Committee on Biological Effects of Ionizing Radiation of the Natl. Academy of Sciences; Univ. of California at Los Angeles (R. Elashoff); New York Univ. Med. Center (R. Shore); Univ. of Chicago (A.B. Schneider); Cancer Inst. of the Chinese Academy of Med. Sciences (J.Y. Li)

LAB/BRANCH

Biostatistics Branch

SECTION

Epidemiologic Methods Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.4	2.0	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Major efforts included: 1) collaboration with the Committee on Biological Effects of Ionizing Radiation of the National Academy of Sciences to evaluate available data on risk to alpha-emitting radionuclides. 2) analysis of the interactive effects of joint carcinogen exposures in large rodent studies, 3) the planning and implementation of cohort and case-control studies in China to quantify the joint effects of smoking and exposure to arsenic and radon on lung cancer risk and to investigate risk factors for penile cancer, 4) studies on the effects of ultraviolet radiation on skin cancer, 5) evaluation of case-control data on dietary risk factors for esophageal cancer, 6) collaboration and consultation on the design and analysis of cohort studies in groups at risk of acquired immunodeficiency syndrome (AIDS), 7) joint evaluation of serum markers for lung cancer, 8) consultation with the Division of Cancer Prevention and Control, NCI, on large-scale prevention and intervention trials, 9) evaluation of cancer risk from occupational exposures in Montreal, 10) evaluation of leukemia risk following treatment of ovarian cancer, 11) evaluation of thyroid cancer risk in persons exposed to head and neck radiation in childhood, and 12) evaluation of the risk of early menopause in a cohort of survivors of childhood cancer.

Project Description

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

M. Gail	Head, Epidemiol. Methods Section	BB	NCI
T. Fears	Mathematical Statistician	BB	NCI
J. Lubin	Health Statistician	BB	NCI
J. Benichou	Guest Researcher	BB	NCI
S. Wacholder	Senior Staff Fellow	BB	NCI
D. Byar	Chief	BB, DCPC	NCI
J. Goedert	Cancer Expert	EEB	NCI
W. Blattner	Chief, Viral Epidemiology Section	EEB	NCI
J. Byrne	Visiting Associate	CEB	NCI
J. Boice	Chief	REB	NCI
E. Ron	Senior Staff Fellow	REB	NCI
C. Land	Health Statistician	REB	NCI
L. Brinton	Head, Environmental Studies Section	EEB	NCI

Objectives:

To promote the use of sound methodology in a wide range of observational and experimental studies by collaboration or consultation and to examine ongoing studies in order to find areas that require new methodological research. Section members may offer extensive support for the experimental design, data management, and analysis of selected studies.

Methods Employed:

Standard and innovative biostatistical and epidemiological procedures are used, as required.

Major Findings:

Dr. Lubin made a major contribution to the report of the Committee on the Biological Effects of Ionizing Radiation (BEIR IV) of the National Academy of Sciences. That report revised estimates of risk from alpha-emitting radionuclides, particularly radon and radon progeny, based on a review of the literature and on a combined reanalysis of primary data from four cohorts. Models for the joint effects of radon and smoking were also reassessed. Dr. Lubin has expanded on the implications of the risk models used in that report in two papers to be published. Drs. Lubin and Gail are collaborating with staff from the Radiation Epidemiology Branch and extramural researchers to reassess thyroid cancer risk in six cohorts exposed to radiation of the head and neck. In a separate project, Drs. Gail and Lubin, in collaboration with Dr. Arthur Schneider and others at the Michael Reese Hospital, analyzed cases of thyroid cancer following irradiation to detect familial susceptibility to radiation exposure. The statistical procedures used were novel and were based on an analysis of intrafamilial correlations of residuals derived from the integrated hazard in a proportional hazards model. Drs. Fears and Gail are collaborating

with Dr. Byrne of NCI's Clinical Epidemiology Branch to quantify the risks of early menopause in women who received radiotherapy and/or chemotherapy for cancer before age 19.

Dr. Lubin is analyzing prevalent case-control data on the joint risks for lung cancer of smoking, arsenic and radon exposures in tin miners in Gejiu City, China.

Dr. Fears has written three papers with Professor Robert Elashoff of UCLA and with Dr. Marvin Schneiderman (National Academy of Sciences) to describe the interactive effects of joint exposures to carcinogens in rodent assays. This work used tests for interaction that were recently developed for survival data.

Dr. Fears also collaborated with Mr. Scotto of NCI's Biostatistics Branch on the risks of exposure to solar ultraviolet radiation (UVB). A manuscript described the calibration of measurements and secular trends in UVB at eight monitoring locations. In another published paper, quantitative estimates of melanoma risk associated with UVB were not altered much by adjustment for potential confounders measured in random samples of controls at these UVB monitoring locations.

Dr. Wacholder is collaborating with other members of the Biostatistics Branch on an analysis of risk factors for esophageal cancer in Linxian, China. The case-control data in this study do not indicate an association with ingestion of pickled vegetables, as had been conjectured.

Dr. Wacholder, in collaboration with workers at McGill University, has published two papers on data from a case-control study to determine whether liquids derived from petroleum carry occupational risks for specific sites of cancer.

Models for projecting risk for breast cancer for women with several known risk factors have been refined by Dr. Gail and his collaborators in the Division of Cancer Prevention and Control. Dr. Lubin included individualized and population risk projections for exposure to alpha-emitting radionuclides in the report of the BEIR IV Committee.

Dr. Gail is supporting efforts of the Family Studies Section to study the natural history of AIDS. He is participating in a cohort study of mothers and infants at risk of developing AIDS. He is also collaborating in a study of a cohort of hemophiliacs, whose dates of seroconversion may be determined from stored sera. Dr. Gail assisted in the analysis of data on the risk of disease among laboratory workers exposed to human immunodeficiency virus (HIV). Another analysis delineated risk factors for the spread of the HTLV-I virus. Dr. Gail serves as Chairman of the Operations Committee that monitors the progress of a placebo-controlled clinical trial of azidothymidine, sponsored by the Veterans Administration, among patients with AIDS-related complex.

Dr. Gail coauthored a collaborative paper that concluded that currently available serum markers to diagnose local lung cancer have limited clinical utility. Dr. Gail consults with members of the Division of Cancer Prevention and Control on the design of large-scale randomized studies to evaluate dietary interventions for the prevention of breast cancer and interventions to reduce smoking.

Dr. Benichou was a coauthor on three reports of clinical trials for lung cancer and chronic lymphocytic leukemia. He is also applying his newly developed methods of statistical inference for attributable risk to risk factors for bladder cancer, in collaboration with members of the Analytical Studies Section and Environmental Epidemiology Branch.

Staff members also provided numerous consultations on statistical methodology and computer methods during the year.

Publications:

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Scotto J, Fears TR. The association of solar ultraviolet and skin melanoma incidence among caucasians in the U.S. Cancer Invest 1987;5(4):275-83.

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ANNUAL REPORT OF

THE CLINICAL EPIDEMIOLOGY BRANCH
EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1987 through September 30, 1988

Clinical epidemiology is a form of observational research in which one must make the most of natural occurrences to determine the causes and mechanisms of diseases. Specifically, the Clinical Epidemiology Branch seeks peculiarities in the occurrence of cancers in persons, families, communities or industries that may lead, in conjunction with recently developed laboratory research, to new knowledge of biology. In this way, study of human disorders may illuminate areas for which no animal models exist. Such observations may lead to new concepts of early detection and prevention.

The retirement of F.W. McKay in July 1988 is a major loss. In his 18 years with us he made an immense contribution on the technical side of mapping, graphing and tabulating U.S. cancer mortality by county and nationally in the creation of atlases. He used this resource to test hypotheses concerning radiation fallout, to innovate in graphic displays of the data, and to study peculiarities in the distribution of the population due to aggregation of young adults in colleges, military camps or prisons. He also played a major role in developing an atlas of neoplasms in domestic animals, as detected by the Branch's former Veterinary Medical Data Program.

Frederick P. Li, M.D., gave the Rosenthal Lecture at the annual meeting of the American Association for Cancer Research. John J. Mulvihill, M.D., received a PHS Meritorious Service medal for his work in the genetics of human cancer, and Robert W. Miller, M.D., gave the annual Nakahara Memorial Lecture in Tokyo.

Ricardo Haupt, a Genovese, spent 3 months with us as a Visiting Scientist, during which he analyzed data from the five-center study concerning late effects of childhood cancer and learned that more than 50% of childhood cancer survivors smoked cigarettes. The support staff was greatly strengthened by the recruitment of Sadie B. Holmes as a secretary and Mai T. Tran as a clerk-typist (stay-in-school).

Highlights

- The familial breast cancer-sarcoma (Li-Fraumeni) syndrome, delineated by the Branch in 1969, is the source of specimens for laboratory research that should reveal the mechanism through which certain diverse cancers aggregate in families or as multiple primary neoplasms.

- A new element in polyposis of the colon has been identified--hepatoblastoma in children of families whose genetic predisposition to polyposis can be recognized by a black spot in the fundus of the eye.

- Mesothelioma, observed in men who had made asbestos-containing cigarette filters, was the basis for a study which revealed that among 35 workers at the factory, mesothelioma developed in five, lung cancer in seven, and fatal asbestosis in four.

- The high frequency of second primary cancers in children who survive retinoblastoma is being more accurately defined by follow-up of 1200 of these survivors, with studies to be made of the later cancers to determine if they show the same gene deletion/inactivation that is typical of retinoblastoma.

- Among about 34,000 veterans who had been on hemodialysis, a substantial excess of renal cell carcinoma was found, and an excess of melanoma apparently also occurred.

- Patients with cystic fibrosis who survive to 30 years of age apparently have an increased frequency of a rare neoplasm, carcinoma of the small intestine, reported in three cases, and has previously been described in non-tropical sprue, another disorder with steatorrhea (fatty stools).

- Elevated alkaline phosphatase levels, found coincidentally in blood chemistry profiles of a pair of adolescent siblings, was not a sign of cancer of bone or liver, as it often may be, but was due to a benign genetic disorder; prompt recognition of such cases can save their families the cost of extensive diagnostic tests and unnecessary worry about malignancy.

- Interdisciplinary studies of single gene traits that predispose to cancer have revealed a new DNA probe that may overlap the gene for von Recklinghausen neurofibromatosis found in families to be on chromosome 17q11; flanking probes will expedite fine mapping of the loci for neurofibromatosis type 2 on chromosome 22q and multiple endocrine neoplasia type 1 on chromosome 11q.

- In collaboration with the Fogarty International Center, guidelines were developed to expedite cancer prevention and control through applying population, clinical, and molecular genetics.

- Continuing analysis of a five-center follow-up study of 2300 survivors of childhood and adolescent cancer shows (in comparison to their brothers and sisters) equal educational achievements (except for brain tumor patients); equal smoking rates; 14% fewer marriages; 15% fewer first pregnancies in those who married; and no excess of cancer, birth defects, or genetic disease beyond expected hereditary cancers.

- Members of the Branch continued to serve as Chairman and Executive Officer of the Advisory Committee for the Air Force (Ranch Hand) study of the health of its personnel who sprayed Agent Orange as a defoliant during the Vietnam War; the Committee reports its evaluations to the Cabinet Level Agent Orange Working Group, chaired by the Under Secretary for Health, DHHS.

- Branch staff consulted on a worrisome leukemia cluster among Japanese children who had received human growth hormone treatment for pituitary deficiency; the meeting of specialists was convened by the Lawson Wilkins Pediatric Endocrinology Society and the European Society for Paediatric Endocrinology.

- Fifty thousand World War II soldiers who developed hepatitis B infection from contaminated yellow fever vaccine continue to be the focus of studies to determine the relationship of the infection to hepatocellular carcinoma later in life (expected but not yet observed).

- In the development of new epidemiologic resources, progress is being made in securing information from other government agencies to simplify follow-up and the determination of occupational category.

- Consultations, advice and analytical reviews continue concerning the effects of ionizing radiation, from the atomic bombs in Japan to Chernobyl and the Brazilian accident involving contamination of people who broke open an abandoned canister containing cesium-137.

- "Rare Events as Clues to Cancer Etiology," was the subject of the 18th annual symposium sponsored by the Princess Takamatsu Cancer Research Foundation, co-organized by the Branch, which edited the proceedings and published a summary report of the meeting.

OFFICE OF THE CHIEF

New Clinical Observations

A third case of ileal carcinoma was found in a 30-year-old survivor of cystic fibrosis of the pancreas. There are only about 1300 such survivors this age or older in the United States. Small intestine carcinoma (and lymphoma) occur excessively in non-tropical sprue, another disorder with impaired absorption of fat. Possibly slow transit time keeps fecal carcinogens in prolonged contact with the bowel wall.

Studies were completed and a paper prepared for publication concerning a family in which two adolescent siblings had elevated alkaline phosphatase levels, often a sign of liver or bone cancer. In this instance, the elevated levels were due to a benign genetic disorder, knowledge of which can lead to prompt diagnosis and avoidance of an extensive search for cancer.

Progress was made in readying for publication data from a series of about 540 cases of the broad thumb/hallux syndrome of Rubinstein-Taybi. Some cancer was observed in this syndrome, but of greater interest were 21 keloids, 5 (possibly 10) of which occurred spontaneously and not due to trauma, the usual antecedent of keloids. Why these children are so prone to hypertrophied scar tissue needs to be explored for clues to the mechanism of this overgrowth.

Renal Dialysis and Renal Cell Carcinoma

Several reports have appeared concerning renal cell carcinoma among patients on hemodialysis. In Japan, a national study revealed 119 cases among 66,000 persons on hemodialysis, particularly after three years of this therapy. Through the use of computer-accessible data on diagnoses among U.S. military veterans, we were able to determine the frequency of type-specific cancers among about 16,000 veterans, 1969-1985. Forty-three developed renal cell carcinoma after dialysis was started. A smaller excess of melanoma appears also to have occurred. The hospital records of these men are now being examined to verify the diagnoses and the sequence of events.

Demography

Cancer Mortality Data: New groupings of counties according to criteria used by the National Center for Health Statistics are being prepared to determine if they provide further information about socioeconomic influences on cancer mortality. A novel graph has been developed, the use of which can provide quick recognition of regional differences in proportionate mortality from three categories of disease examined together. A report has been submitted for publication, and another has been prepared on marked excesses of young adults living in counties having colleges, military bases or prisons. Appreciation of these age-related peculiarities in the population distribution is relevant to studies of disease rates in the young, such as AIDS.

Radon: Tabulations are just being completed for a study of 11 forms of cancer among people living in the Reading Prong, an area that cuts across 15 counties with high levels of radon. The Prong runs from lower New York State through New Jersey to Pennsylvania. According to theory based on the experience of uranium miners, radon may induce lung cancer that could account for up to 10,000 deaths annually in the United States. The analysis of our tabulations will be made by the Radiation Epidemiology Branch.

Nuclear Reactors: There has been much concern that cancer rates may be raised among people who live near nuclear reactors. A study is therefore being made by the Radiation Epidemiology Branch of cancer mortality in the areas surrounding about 100 U.S. nuclear reactors. Our Branch is helping to provide the data for this endeavor.

Agent Orange

Dr. Robert Miller served for the fifth year as the Chairman and Dr. Julianne Byrne as the Executive Officer of the Advisory Committee for the Air Force (Ranch Hand) study of the health of its personnel who sprayed Agent Orange as a defoliant in Vietnam. The Committee reports to the Cabinet Level Agent Orange Working Group, chaired by the Under Secretary for Health, DHHS. During the year an evaluation was made of a report concerning the health of the men as revealed by the first follow-up medical examination. No findings were attributed to Agent Orange exposure. The Centers for Disease Control has developed a method for determining the blood level of dioxin. Study of about 150 exposed personnel and 50 unexposed personnel revealed the average dioxin level to be ten times greater in exposed personnel than in controls. The half-life was 7.1 years. The other men in the study, a total of about

2200, will have dioxin levels determined, after which their health status can be evaluated with respect to their blood dioxin levels.

Leukemia Cluster and Human Growth Hormone Therapy

In Japan five children developed leukemia, four of them since 1985, from treatment with human growth hormone for pituitary deficiency. An attempt to replicate the Japanese findings elsewhere was made. No cases were found in Australia or Canada, and the three that occurred in the United States were after radiotherapy for craniopharyngioma. In Europe, however, six cases were found but two of them had very short intervals between the initiation of hormone therapy and diagnosis of leukemia. All but two of the cases had acute lymphocytic leukemia. The situation will be closely watched for further cases. Meanwhile, no decision could be reached about a causal relationship (Lancet 1:1159-1160, 1988).

Virus Studies

Liver Cancer after Hepatitis in Veterans of World War II: This three-phase study of the largest outbreak of hepatitis B virus (HBV) on record is aimed at clarification of the association between HBV and primary hepatocellular carcinoma (PHC). As reported in the New England Journal of Medicine in April 1987, the first phase, a serologic survey of 618 Army veterans, provided definite evidence that the 1942 epidemic was caused by HBV. The survey was also remarkable for the infrequency with which hepatitis B carriers were found, for the persistence of hepatitis B markers 43 years after the epidemic, and for high HBV antibody titers.

The second phase of the study, now nearing completion, examined the mortality of soldiers who developed hepatitis after yellow fever vaccination, as compared with others who were vaccinated but did not develop hepatitis, and a third group which entered the Army after use of the contaminated vaccine was discontinued. Death certificates were obtained for the 60,000 Army veterans in the study who died since January 1, 1946. The three cohorts are being compared as to cause-specific mortality, with emphasis on deaths attributed to diseases of the liver, including 63 with death certificate diagnoses of liver cancer.

The third component, a case-control study of Veterans Administration (VA) hospital discharges for liver cancer vs. matched hospital controls, is nearing completion. The hospital records had to be reviewed because less than half of those coded to liver cancer had clinical evidence of PHC. The VA files initially identified over 5000 veterans with liver cancer, but the number with immunization records available will be much less because so many were lost in a fire at the St. Louis records center in 1973. These records are needed to identify which men received vaccine from contaminated lots. We do not yet know if enough records with vaccine lot numbers can be obtained to determine how the findings for the case-control study compare with those in the cohort mortality study.

Since the preliminary indications of the cohort mortality study suggest that any excess PHC attributable to the HBV infection may be small, a review is being made of a roster of about 2,500 veterans with service-connected VA compensation in 1957 for residuals of hepatitis to determine its usefulness in the investigation of the relation between HBV infection and PHC. Attention has also been directed to a sample of Red Cross blood donors for which an incomplete mortality follow-up suggests a heightened risk of hepatoma among about 15,000 carriers.

Radiation Studies

Two members of the Branch have diverse activities concerning radiation exposures or effects. Dr. Gilbert Beebe is a member of a group appointed by the National Research Council to advise on the design and conduct of a study of veterans exposed to nuclear tests (CROSSROADS) in the Marshall Islands in 1946. He is also the DHHS representative on the Science Panel of the Committee on Interagency Radiation Research and Policy Coordination which is in the Office of Science and Technology. During the year it considered how the VA might best use the NIH Radioepidemiological Tables to adjudicate claims by veterans that their cancers were due to ionizing radiation exposure while in military service; whether to plan before nuclear disasters for research on human health effects to be performed after such a disaster; whether Federal agencies should be advised to change the quality factors used for neutrons from 10 to 20, as some have proposed; whether a criteria document prepared by the National Institute for Occupational Safety and Health (NIOSH) was based on the best information available on the risk of lung cancer from such exposure; whether to issue a report on the health effects from exposure to non-ionizing radiation; how to encourage the development of better risk estimates on the effects of exposure to neutrons; how to evaluate various reports on the risk of lung cancer from exposure to radon; and how the Federal Radiation Research Agenda for 1985 compared with that for 1981.

Dr. Beebe also monitored preparation of a report on the human health effects of ionizing radiation that is being prepared by a committee of the National Academy of Sciences. He helped organize and chaired an international workshop on the interface between radiation protection standards and radiation epidemiology, convened by the Organization for Economic Cooperation and Development in Paris.

For the Radiation Effects Research Foundation, Dr. Beebe reviewed manuscripts and research protocols, made recommendations concerning the program, and visited Hiroshima and Nagasaki to attend the meeting of the Science Council and a special workshop on radiation susceptibility, and to participate in the ceremonies marking the 40th anniversary of the founding of the Atomic Bomb Casualty Commission. Dr. Beebe also has in press in Cancer Investigation an invited paper on highlights of the research on A-bomb survivors in Japan.

Dr. Beebe is a member of the Task Group on Comparative Carcinogenicity of the National Council on Radiation Protection and Measurements. He was a regular project site visitor to the University of Utah for the NCI Radiation Effects Branch's large contract for studies of leukemia and thyroid cancer in relation to fallout from the nuclear weapons tests at the Nevada Test

Site in the 1950s. He was also a member of the Technical Advisory Panel for the Nuclear Shipyard Workers Study at the School of Public Health, The Johns Hopkins University. He attended the weekly staff meetings of the Radiation Epidemiology Branch to help with critiques of new proposals, manuscripts, and other items. Together with Dr. Boice of the NCI's Radiation Epidemiology Branch, he was instrumental in persuading the Nuclear Regulatory Commission to establish a registry of nuclear power plant workers containing identifiable demographic data, and dosimetric information of adequate quality and detail to support follow-up studies.

In connection with his duties as Assistant Project Officer for the Thyroid Nodule Study in Guandong Province, China, Dr. Beebe participated in the review and write-up of the data developed from the examination of 2,000 women in the high- and the low-background areas of that province. He also consulted in Brazil on the accident there involving spread of cesium-137 among people who broke open a container from an abandoned radiotherapy machine.

Dr. Miller is on the Science Council of the Radiation Effects Research Foundation and is playing an active role in organizing special workshops designed to strengthen the future scientific program. He is on the Scientific Review Committee of the Division of Biological and Medical Research, Argonne National Laboratory, and the Epidemiology Advisory Committees of the Hanford and the Los Alamos National Laboratories. He is also chairman of the National Council on Radiation Protection and Measurement Scientific Committee 76, concerned with the effects of radiation on the embryo and fetus, and has in preparation a report that will be published in the series of the Council.

Epidemiology Resource Development

As chairman of an NCI Working Group on data resources, Dr. Beebe plays an active role in developing new resources for cancer epidemiology and in improving access to existing information, especially administrative records of Federal agencies. His efforts have led to a broadening of access to the address file of the Internal Revenue Service for NCI investigators of occupational cancers and may further widen the range of medical research for which the Intrnal Revenue Service will provide current addresses.

The NCI Working Group is making a major effort to create a national reporting system or data base for studies of occupational cancer. In one study, for which Dr. Beebe serves as Project Officer, there is an interagency agreement with the Social Security Administration (SSA) to retrieve SSA employment histories of individuals who have died of mesothelioma and of controls, the objectives of which are: (1) the feasibility and cost of retrieving SSA information from quarterly earnings reports formerly submitted by employers as the basis for eligibility for SSA benefits and (2) a comparison of the SSA information with that obtained from next-of-kin. This study has been hampered by the privacy concerns of SSA and IRS, and only this year was a tape obtained from SSA for analysis. The information on feasibility and cost of retrieval has been written up and the tape containing SSA and next-of-kin information on employment history is currently being analyzed. It is now evident that the cost of reconstructing employment histories from SSA files prior to the change from the quarterly

earnings report to the W-2 form is high enough that it can be used only for small samples of high priority. It also seems clear that the next-of-kin employment histories are very incomplete in comparison with those assembled by SSA. The current analysis should identify some of the variables that influence the completeness of histories obtained from next-of-kin.

Under another agreement with SSA, for which Dr. Beebe serves as Co-Project Officer, the SSA Continuous Work History Sample (CWHS) of SSA registrants is being studied as a possible data base for studies of cancer mortality in relation to employment history. Death certificates have been obtained for the period 1973-1977, and cause-of-death coding is being provided under a subcontract with the National Center for Health Statistics (NCHS). In addition, the Census Bureau is coding the death certificate information on usual occupation and employment. Analysis of the material is expected to show whether the one percent CWHS, with its employment information dating back to 1957, is likely to be a fruitful source of information on mortality differentials associated with employment history. The data will also be used a) to explore the quality of employment history information on the death certificate itself, about which there is considerable concern; and b) to create mortality tables for employed workers that epidemiologists may wish to use, in addition to the rates for the entire population, to take account of the "healthy worker effect" on mortality rates.

Because the SSA data on employment do not include information on specific occupation, which is on income tax forms, NCI has an interagency agreement with IRS to code its Statistics of Income sample for 1979 as to occupation in an attempt to refine the SSA data on industry of employment for that year, and to obtain death certificates for the period 1979-1984. The resulting file should show whether adding the IRS information on occupation will enhance the value of the SSA information on industry of employment as a source of mortality differentials. This work has been slow because it was difficult to overcome the resistance of some States to sending death certificates to IRS which is making the comparison, but is not known as a producer of health statistics. These difficulties have now been resolved. The IRS file will also be used to compare IRS and SSA information on occupation and industry with that on the death certificate as coded by the Census Bureau. Good progress is being made in the transfer of cause-of-death information from NCHS and the coding by Census of industry of employment and occupation on the death certificate, but certificates from the last two States (New York and Virginia) are only now being acquired.

Representatives of IRS and SSA meet periodically with Dr. Beebe to devise some way of transmitting CWHS information to NCI for its restricted use. Although progress has been made in these discussions, IRS has yet to approve the draft agreements that have been formulated.

Ultimately it is hoped that the death certificate information on industry of employment and specific occupation will be improved in quality, coded by the states, and sent to NCHS for incorporation in the National Vital Statistics System.

Dr. Beebe and other members of the Epdidemiology and Biostatistics Program have been active in providing funds through NIOSH for training state coders and compensating a growing number of states for sending coded information to

NCHS. A tape file of deaths in 12 states during 1984 has been provided to NCI and a manuscript is being prepared for publication by NCHS. Because NCHS has not been successful with its budget process in maintaining and expanding this work, NCI has communicated to CDC the importance of the program and has encouraged them to take an active role during the budget process so that NIOSH and NCHS can further develop the program.

Dr. Beebe is one of the NIH advisors to the Director, NCHS, in the management of the National Death Index (NDI) and has assisted Dr. John Boice of the NCI Radiation Epidemiology Branch in exploring the feasibility of extending the Index back in time, perhaps to 1960. It now covers only deaths since 1979. For most cohort studies investigators require information on deaths well before that time. Dr. Beebe also chairs an NCI Working Group on NCI policy with respect to the NDI. Its goal is to ensure that NCI studies needing access to the NDI in future years shall have stored the individual identifiers needed by the Index for efficient searching. The Working Group has formulated a recommendation that is about ready to go to Dr. DeVita for his consideration.

U.S.-Japan Cooperative Cancer Research Program

Our responsibility for the Interdisciplinary Area of this Program led to two workshops during the year. One concerned melanoma, which is rare in the Japanese, in part because of an apparent low frequency of the genetic disorder, dysplastic nevus syndrome (DNS), and partly because of skin pigmentation and shielding from sun exposure. To confirm the low frequency of DNS among the Japanese, arrangements were made with the Radiation Effects Research Foundation in Hiroshima and Nagasaki to screen for these lesions in a large-scale skin cancer survey of atomic bomb survivors which is to begin soon. Standardized photographs of the backs of the subjects and of suspicious lesions will be sent to the Family Studies Section of the Environmental Epidemiology Branch, which specializes in studies of DNS. Among U.S. white patients with melanoma, about half have evidence of DNS in their primary skin lesions, which occur particularly on the neck, trunk, arms, and legs. By contrast, the Japanese have a relatively high frequency of melanoma of the palms and soles, especially under the nails of the thumbs and great toes. A highlight of the workshop was a presentation by the Emperor's younger son, Prince Hitachi, whose research at the Cancer Institute in Tokyo concerns melanoma in giant goldfish (carp), which frequently develop black, red or iridescent cancers late in life. The other workshop concerned the Li-Fraumeni syndrome (familial breast cancer and soft-tissue sarcoma). The purpose was to seek new ideas for study and to determine if in Japan, where no cases have been reported, the syndrome could be found in tumor registries of various types. Families that may have the syndrome were identified in the All-Japan Childhood Tumor Registry and in a large breast cancer series at the Cancer Institute in Tokyo. Other families with unusual cancer aggregation were observed in these series and at the National Cancer Hospital in Tokyo. Arrangements are being made for Yukiko Tsunematsu, M.D., of the National Children's Hospital in Tokyo to spend a month with Louise C. Strong, M.D., at M.D. Anderson Cancer Center in Houston, Texas to develop further Dr. Tsunematsu's case-series. The exchange visit will be under the U.S.-Japan Cooperative Cancer Research Program.

Plans are being made for two workshops during the coming year, one on biostatistics of cancer and the other on the use of data from tumor registries relevant to cancer prevention and control.

International Cancer Symposium

"Rare Events as Clues to Cancer Etiology" was the title of the 18th annual international cancer symposium sponsored by the Princess Takamatsu Cancer Research Foundation. Because this subject has been a favorite of NCI epidemiologists, four presented their work, and Drs. Robert Miller and Joseph Fraumeni served as the foreign co-organizers of the symposium. Dr. Miller played a main role in preparing the proceedings for publication, and has published a summary report of the meeting.

CLINICAL STUDIES SECTION

A unit of the Branch has been in Boston since 1953, where it has had access to a wide array of etiologically interesting cases in the clinics and on the wards. Cases in the past have been studied through the use of hospital records. Collaboration with laboratory scientists has been exceptionally close in recent years. Furthermore, the Section, by the example it has set of the research benefits that can come from observational research, has attracted students, physicians-in-training and other health professionals as volunteers in its activities.

Hereditary Cancers of the Genitourinary Organs

Additional studies continue to be made of a family with 10 cases of renal cancer, and a translocation between chromosomes show that the c-myc oncogene on chromosome 8q24 had moved to the derivative 3 and that the RFLP, D3s2, was rearranged to the derivative 8. However, pulse field gels show that c-myc is not within 700 kb of the breakpoint. Studies of chromosome 3 by several groups have shown chromosome 3p rearrangements in renal cancer tissues of non-familial cases, suggesting its importance in the development of this neoplasm. Several polymorphic fragments (D1S1, D3S2 D3S3) have been mapped to the region 3p14-21, and these and other polymorphic probes are being used to further localize the breakpoint on chromosome 3 in our family. The hypothesis is that the gene on 3p involved in the development of human renal carcinoma is at the breakpoint of the t(3;8) in our family.

The Familial Breast Cancer-Sarcoma Syndrome

Since initial identification of this syndrome in 4 kindreds in 1969, additional affected families have been ascertained by members of the Branch. An analysis of 24 of these families has clarified the clinical features of the disorder. The inheritance pattern is autosomal dominant, with cancer expressed by 45 years of age in most affected family members. The tumor types present in these families include sarcomas of bone and soft tissue, acute leukemia, brain tumor, adrenocortical carcinoma and breast cancer. Investigations are in progress of 13 additional families that appear to have the syndrome. Laboratory studies of affected family members have started to

reveal insights into the pathogenesis of this syndrome. Cytogenetic studies of soft tissue sarcomas from familial and sporadic cases show correlations between chromosomal translocation and histological subtype of the sarcoma. These include the translocation, t(X;18), in synovial sarcoma, deletion of chromosome 11p in rhabdomyosarcoma and translocation between chromosomes 12 and 16 in liposarcoma. The findings may be useful in classifying poorly differentiated soft tissue sarcomas, and to localize genes involved in the development of sarcomas. In addition, studies of the recessive oncogene Rb1 (from human retinoblastoma) has shown homozygous deletions in 3 of 16 soft tissue sarcomas.

Mesothelioma in Cigarette Filter Makers

We recently observed mesothelioma in 3 men who had made cigarette filters which contain asbestos. All had worked for one small company between 1951 and 1958. According to the patient, the cigarette filter contains 5 to 30 percent blue asbestos, or crocidolite. An additional 35 workers at this plant have been identified and 5 cases of mesothelioma, 7 lung cancers, and 4 fatal asbestosis were found.

Delineation of New Cancer Susceptibility Syndromes

Work is in progress to identify new cancer susceptibility syndromes, and variants of previously recognized syndromes. In studies of dominantly transmitted polyposis coli, 4 families were found in which a child has developed hepatoblastoma. This association was first described in England several years ago. In Boston, one child with hepatoblastoma has survived the liver tumor for 5 years. When the association between hepatoblastoma and polyposis was recognized, the child underwent colonoscopy with the finding of early polyps. Three additional members of her family were also found to have previously unrecognized polyposis coli and have undergone colectomy. We have now established a Registry of the Hepatoblastoma-Polyposis Coli Association and have solicited polyposis centers worldwide for additional cases. Twenty have been enrolled to date and collection of specimens for laboratory studies have begun.

In a patient with the newly described syndrome, cystic hamartomas of the lung, a uterine stromal sarcoma developed which showed insertion of chromosome 19 into chromosome 10.

We have recently observed 5 cases of multiple primary cancers that include melanoma and soft tissue sarcoma. Two of them also have dysplastic nevus syndrome (DNS). The possibility that sarcomas are a previously unrecognized feature of DNS is under study.

Late Effects in Survivors of Childhood Cancer

A number of studies have been undertaken to evaluate adverse effects of late onset among childhood cancer survivors. In a 10-year prospective study of second cancers at the Dana-Farber Cancer Institute, 30 new cancers were observed when 2 were expected. All but 2 of the second cancers were solid tumors. The tumors usually occurred within the field of radiation therapy.

The analysis is now being extended to 15 years of prospective follow-up. A seven-hospital study was made of pregnancy outcome in patients treated in childhood for Wilms' tumor. The data show a high frequency of adverse pregnancy outcomes in women who received abdominal radiation therapy for the neoplasm. Among these patients, the rate of adverse pregnancy outcomes was 30%, a rate eightfold above expectation. The adverse outcome included excess neonatal and perinatal mortality and the birth of low-weight infants. These abnormalities were not present in female patients who had not received abdominal radiation. To pursue this unexpected observation, a new series is being gathered of offspring of patients who survived cancers other than Wilms' tumor. The hypothesis is that low birthweight will be observed among offspring of irradiated female patients.

A recent study reported a 90% risk of second cancers, primarily sarcomas, among nearly 800 survivors of hereditary retinoblastoma. However, the risk estimate may be flawed by a high proportion of cases lost to follow-up. To refine the risk, a follow-up study of these cases and 1200 others with retinoblastoma is in progress. The study has provided access to tissue of second cancers in retinoblastoma patients. These tissues will be probed with the newly cloned retinoblastoma gene to study the role of this gene in secondary neoplasms.

The frequency of hypertension has been studied in a series of Wilms' tumor patients who had nephrectomy and other treatments between 14 and 53 years ago. Eighty percent are normotensive. The overall frequency of hypertension did not exceed expectation based on data for the general population. The data provide assurance that hypertension is not a common sequel of treatment for Wilms' tumor.

CLINICAL GENETICS SECTION

The purpose, goals, and objectives of the Section remain the same:

1. To identify genetic factors and disorders associated with human cancer and to promote similar studies worldwide. To document patterns of familial aggregation of neoplasms; to study selected disorders and families by genetic and laboratory investigations in an effort to elucidate carcinogenic mechanisms and the degree to which heredity and the common familial environment contribute to the etiology of neoplasms. To distribute biologic specimens from selected subjects to laboratory investigators for etiologic studies by biochemical, cytogenetic, immunologic, viral, and tissue culture methods. To study, similarly, patients with birth defects and other heritable disorders that may predispose to malignancy.

2. To direct the NIH Interinstitute Medical Genetics Program which provides a multidisciplinary setting in which patients with cancer or at high risk of cancer can be studied and counseled, and in which graduate physicians and medical students can be trained in the diagnosis, counseling, and treatment of individuals with or at risk of genetic disease, and in the research approach to genetic disease.

3. To document fertility and reproductive outcome in patients who become pregnant before, during, and after cancer treatment; for the purposes of testing genetic theories of cancer etiology; defining potential gonadal toxicity of cancer treatment, both teratogenicity and mutagenicity; and providing needed information for genetic counseling of long-time survivors of cancer.

Interdisciplinary Studies of Genetics

Neurofibromatosis

The section continues to be involved in studies to clarify the genetics and natural history of von Recklinghausen's neurofibromatosis (NF1), an autosomal dominant disorder with protean manifestations, including an increased risk of certain cancers. One of our primary goals, that of determining the chromosomal location of the gene for this disease, has been reached. Last year, Dr. Bernd Seizinger, a fellow in the laboratory of Dr. James Gusella at the Massachusetts General Hospital, used DNA from several of our NF1 families to determine that the gene for this disease is located near the nerve growth factor receptor gene on the long arm of chromosome 17. Independent confirmation with anonymous DNA probes came from Salt Lake City. Early studies with the nerve growth factor receptor gene indicated that it was not the site of the primary defect in NF1 since it could be separated from it by crossing over. Further linkage studies by Dr. Seizinger and others suggest that the NF1 gene is located very near the chromosome 17 centromere. Drs. John Mulvihill and Dilys Parry continue to be very involved in linkage studies of NF1. Recently, many laboratory scientists and clinicians have grouped together to form the NF1 Linkage Consortium whose goal is to map precisely the NF1 gene.

To do this, Consortium members have exchanged DNA probes and are using them to examine DNA from NF1 families, especially those in which recombination has occurred between the NF1 locus and a specific marker. This research has two goals: 1) to order the DNA markers with respect to the centromere of chromosome 17, and 2) to map NF1 with regard to these markers. Since the strength of the results for any one probe increases as the number of families analyzed for it increases, Consortium members have agreed to pool their data; the combined data will then be returned to each contributor for independent analysis. To facilitate this endeavor, Drs. Parry and Mulvihill have agreed to receive data from each contributor, compile all the data onto PC compatible diskettes and send these back to the contributors. The results of the separate analyses will be presented at a meeting of the Consortium in late June. This remarkable collaboration is expected to greatly shorten the time necessary to localize the NF1 gene.

During this year, the Section's interest in the neurofibromatoses expanded to include NF2, an autosomal dominant disorder recently mapped to chromosome 22. Its major feature is the occurrence of bilateral acoustic neuromas.

These are actually Schwann cell tumors that arise from the vestibular branch of the 8th cranial nerve. These tumors can develop at any time between the second and seventh decade, but most frequently occur in the early to mid-twenties. Since the vestibular nerve is involved in balance, unsteadiness, especially in the dark, is often the earliest manifestation of a tumor's presence. In addition, pressure from a growing tumor frequently damages the adjacent cochlear and facial nerves, resulting in deafness and facial paralysis. Early diagnosis clearly provides the best opportunity for successful treatment with the least risk to cochlear and facial function.

Future study may now be facilitated by the use of three recent advances: 1) the availability of DNA markers for chromosome 22, which may be used to identify gene carriers within affected families; 2) the knowledge that presenile lens opacities may occur in gene carriers prior to tumor development; and 3) the ability to visualize very small tumors with the use of magnetic resonance imaging. We have utilized a combined clinical and molecular genetics approach in evaluating a three generation kindred with NF2 that was last studied 14 years ago. To date, we have drawn blood for gene linkage studies on 41 individuals, of whom 23 have undergone detailed clinical examinations and magnetic resonance imaging.

Eleven people have acoustic neuromas; in six, they had been diagnosed previously; in five, the tumors were diagnosed at NCI through magnetic resonance imaging. The mean age of those already known to have tumors is now 61 years, versus 33.6 years in the latter group. Five of the six individuals with previously diagnosed tumors had surgery; four were deaf in the operated ear(s) and had profound hearing loss on the untreated side from tumor. The youngest patient in this group had very small tumors that had not yet affected his hearing. Normal hearing was also present in four of the five individuals with newly diagnosed tumors. The fifth person in this group was a 70-year-old man who had experienced progressive hearing loss of five years duration.

Five of the six persons with known tumors had presenile posterior lens opacities or cataracts as did three of the newly diagnosed cases, including a 19-year-old man in whom a cataract was visible with a hand-held ophthalmoscope. The three without posterior lens opacities were ages 21, 25 and 27, so posterior lens changes may yet occur in them. The DNA studies have not yet been completed; when they are, we will be able to compare them with the clinical observations to determine the efficacy of the imaging, audiologic and ophthalmologic screening procedures.

These observations illustrate how gene localization (mapping) has led to a means for early diagnoses and treatment, which can prevent disability or death.

Interinstitute Medical Genetics Program

In support of many of the above efforts, Drs. Mulvihill and Parry continue to direct the NIH Interinstitute Medical Genetics Program, including its clinical services and training program for 8 Fellows and up to 12 medical students. Actual numbers of patients seen in the clinic who had or were predisposed to tumors were:

Bilateral acoustic neurofibromatosis (NF2)	30
von Recklinghausen's neurofibromatosis	21
Familial pheochromocytoma	18
Women at high risk of breast cancer	8
Familial hypereosinophilia leukemia	5
Down's syndrome	4
Familial acute myelogenous leukemia	2
Cowden's disease	1
Multiple skin cancers	1
Ataxia-telangiectasia	1
Multiple endocrine neoplasia type 1	1
Total	92
Birth defects or familial syndromes	17
Grand total	109

Reproduction and Human Cancer

The Five-Center Study

To investigate the late effects of cancer and its therapy on the health of long-term survivors of childhood or adolescent cancer, we interviewed 2283 survivors and 3270 of their siblings as controls about their health, their reproductive experiences and the health of their children. Survivors were diagnosed between 1945 and 1975; they had to have survived more than five years after the diagnosis of their first malignancy and to have reached age 21. The study was done in collaboration with scientists from Yale University, the Universities of Iowa and Kansas, the California State Department of Health Services and M.D. Anderson Hospital of the University of Texas. Our results apply to survivors who were diagnosed up to the time when childhood cancer became a curable disease, and who had reached their reproductive years.

Several manuscripts regarding different issues of concern to childhood cancer survivors were published in leading journals, and others have been accepted for publication. With regard to fertility, we found that cancer survivors who have no known cause of infertility have only 83% of the fertility of their sibling controls. The fertility of female survivors is only slightly affected by alkylating agents, while male fertility is reduced by half. Radiation below the diaphragm, without alkylating agent treatment, reduced fertility in both sexes by about 25%. Among those who did become parents, there are significantly fewer offspring to both male and female survivors than to their sibling controls.

Menopause occurred earlier in survivors compared to their sisters. Risk factors for early menopause were genital cancers, treatment with radiation below the diaphragm and treatment with alkylating agents. The risk of menopause was highest immediately upon treatment, but did not seem to fall off with time elapsed since therapy.

Female survivors of Wilms' tumor were more likely than their sibling controls to have a child with a birth defect or a low birthweight baby. A pregnancy embarked on by a Wilms' tumor survivor had only half the chance of ending in a normal full-term birth, compared to her sister's pregnancy. Female survivors of Wilms' tumor, and perhaps their first-degree female relatives, are more likely than the general population to have a defect of the reproductive tract.

Offspring of men and women treated for other childhood and adolescent cancers were not more likely to be born with birth defects than offspring of their siblings. Familial aggregation of known single gene traits associated with cancer was observed, but otherwise there was no excess of cancers in the children of survivors during the limited follow-up period.

Both male and female survivors were less likely ever to marry compared to their sibling controls. Male survivors were 20% less likely to marry than male controls; female survivors had only a slight marriage deficit. Both men and women who had brain tumors were substantially less likely to marry, men more so than women. Survivors of Hodgkin's disease, men and women together, were slightly less likely to marry. There were no differences in the proportion of divorces, but marriages ending in divorce were shorter by 10 months in survivors.

Survivors of tumors of the brain and central nervous system were less likely to complete the eighth grade, or if they completed high school, to enter college. Twenty percent of survivors did not know that they had cancer. Apart from former brain tumor patients, the proportion who were unaware of their cancer history were more likely to be non-white, to have been diagnosed in earlier years, not to have received alkylating agent therapy and, among our five centers, to have come from the Connecticut center.

Despite their high risk for having another cancer, childhood cancer survivors had almost the same smoking habits as controls, or the general population. No demographic characteristic that we inspected were linked to lower smoking rates; survivors treated with radiotherapy to the chest were the only group with more ex-smokers, presumably due to chest disease after radiotherapy, which was made worse by smoking.

There were no marked deficits in education, earning ability, or marriage rates among 57 retinoblastoma (RB) survivors. However, male RB survivors who earned less than $15,000 yearly were more likely to have separated, divorced or remarried than to be still in their first marriage.

Other Collaborations

We have established a collaboration with the Children's Cancer Study Group, and with the National Institute of Child Health and Human Development, to follow long-term survivors of acute lymphocytic leukemia in childhood. The studies being planned include a retrospective cohort study, similar in design to the Five-Center Study, a study of the health of survivors and their offspring, a clinical study of growth and growth hormone and one of pubertal development in younger children.

Two additional studies are in development, with the purpose of elaborating on the findings of the five-center study that have low statistical power. The first, in collaboration with Oxford University and the International Agency for Research on Cancer, would be an international collection of information on the health of offspring of cancer survivors. The second is a recall of all patients of the National Cancer Institute's Clinical Oncology Program (four Branches), with the objective of looking for germ cell mutation through laboratory assays of protein variants and eventually DNA polymorphisms not manifested as clinical genetic disease.

A monograph derived from a May 1987 International Conference on Reproduction and Human Cancer is in late production stages. In addition, several invited reviews on the topic were prepared.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04377-17 CEB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Familial, Congenital, and Genetic Factors in Malignancy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	John J. Mulvihill	Chief, Clinical Genetics	CEB	NCI
Others:	D. M. Parry	Geneticist	CEB	NCI
	P. Madigan	Research Technician	CEB	NCI
	C.A. Collins	Research Assistant	CEB	NCI

COOPERATING UNITS *(if any)*

Atomic Energy of Canada, Ltd. (M. Paterson); UCLA (R. Sparkes); Biotech Laboratory (S. Tsai); Yale University (U. Francke); Health Research (A. Sandberg); Brookhaven Laboratory (R. Setlow); Litton Bionetics (J. Ivett)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Clinical Genetics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.8	3.0	0.8

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Study of preneoplastic genetic diseases with a high risk of cancer may help detect environmental and genetic influences in carcinogenesis, especially when appropriate laboratory assays are used. Neurofibromatosis, an autosomal dominant disorder with a predisposition to cancer, received emphasis. Results on 12 families show linkage to the gene for the receptor for nerve growth factor, with a lod score of 4.4 at a recombination distance of 14 centimorgans. Forty-year follow-up of 212 neurofibromatosis patients in Denmark permitted life-table analysis: survival was worst for females who were the original probands, slightly better in male probands, and only slightly less than rates expected in the general population in affected relatives. The relative risk for malignant neoplasms was 4.0 in probands, but only marginally elevated in relatives. Similar multidisciplinary approaches to three other preneoplastic syndromes revealed, in the nevoid basal cell carcinoma syndrome, a lod score of 1.2 to amylase 1 on chromosome 1p, and an association with auditory defects; in the dysplastic nevus syndrome, a possible excess of chromosome breaks; on multiple endocrine neoplasia, type 1, no firm linkage to 28 polymorphic protein loci.

Project Description

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged in this Project:

J. J. Mulvihill	Chief, Clinical Genetics	CEB	NCI
D. M. Parry	Geneticist	CEB	NCI
C. A. Collins	Research Assistant	CEB	NCI
P. Madigan	Research Technician	CEB	NCI

Objectives:

To identify genetic factors and disorders associated with human cancer and to promote similar studies worldwide. To document patterns of familial aggregation of neoplasms; to study selected disorders and families by genetic and laboratory investigations in an effort to elucidate carcinogenic mechanisms and the degree to which heredity and the common familial environment contribute to the etiology of neoplasms. To distribute biologic specimens from selected subjects to laboratory investigators for etiologic studies by biochemical, cytogenetic, immunologic, viral, and tissue culture methods. To study, similarly, patients with birth defects and other heritable disorders that may predispose to malignancy.

Methods Employed:

Interviews of patients with cancer or other diseases to ascertain familial occurrences of cancer and birth defects, as well as prior medical and environmental history; documentation of history by reviewing appropriate vital and medical records; collection and distribution of biological specimens from such families. Establishment and maintenance of laboratory collaboration by contract and other means. Invited lectures, reviews, and committee memberships provide ways for stimulating research in cancer genetics.

Major Findings:

Reports published or in press in the last 12 months by the two permanent and two temporary participants of the project comprise 10 reports of original research, 10 reviews, and an abstract for a national meeting. Research reports involved co-authors from the Environmental Epidemiology, Medicine, and Surgery Branches of the National Cancer Institute; the National Eye Institute; the National Institute of Child Health and Human Development; the University of California at Los Angeles; Yale University; Harvard University; Biotech Laboratories, Inc.; and the Institute of Medical Genetics, Copenhagen, Denmark.

Interdisciplinary Studies on Neurofibromatosis. The Section has committed considerable resources to studies designed to clarify the genetics and natural history of neurofibromatosis (NF), an autosomal dominant disorder with protean manifestations including an increased risk of developing certain cancers.

In recent years, the likelihood of determining the location of human genes has been greatly elevated by the rapid increase in the number of DNA restriction fragment length polymorphisms (RFLPs) that have become available for study. Therefore, a few years ago, we established a collaboration with Dr. James Gusella and his colleagues at Massachusetts General Hospital, Boston. This group has been in the forefront in localizing genes causing inherited disease through linkage analysis of segregation patterns of DNA RFLPs. Using DNA from several of our NF families, Dr. Bernd Seizinger, a fellow in the Boston laboratory, has determined that the gene for NF is located near the nerve growth factor receptor gene which is on the long arm of chromosome 17. The nerve growth factor receptor gene is unlikely to be the site of the primary defect in NF since it can be separated from it by crossing over. Independent confirmation with anonymous DNA sequences came from Salt Lake City.

The localization of the NF gene to chromosome 17 has profound implications for both basic research and clinical practice and greatly increases the prospect of identifying the nature of the primary defect in this disorder. Using DNA markers that are located close to and on either side of the NF gene, it should soon be possible to determine the molecular explanation for the high mutation rate in this disorder and to elucidate the mechanism of tumorigenesis. In addition, several clinical goals can be addressed: 1) by typing more pedigrees for these markers, one could resolve the issue of genetic heterogeneity; that is, whether in any families a non-allelic gene, including a gene on a different chromosome, could produce the NF phenotype; 2) prenatal diagnosis could be offered to couples in which one member has NF; and 3) diagnosis of presymptomatic gene carriers should be possible. Since the ability to correlate clinical manifestations with changes at the DNA level will soon be realized for NF, we intend to continue evaluating families with this disorder, especially those in which an increased susceptibility to malignancy is a predominant feature.

Abbreviated reports have been made of a 39-year follow-up of 212 NF patients in 84 kindreds. To minimize the effect of ascertainment bias, which has plagued all previous patient series, standard life-table analyses were done separately for probands and their affected relatives. In comparison with the general population, survival rates were significantly impaired in relatives with neurofibromatosis, even worse in probands, and worst in females who were probands. Malignant neoplasms, including benign central nervous system tumors, occurred in 45% of the probands, giving a relative risk (RR) of 4.0 (95% confidence intervals [CI]: 2.8, 5.6), compared to expected numbers calculated from the person-years-at-risk and incidence rates for the Danish Cancer Registry. Female relatives had slightly higher cancer rates (RR 1.9; CI: 1.1; 3.1), whereas male relatives did not differ from the general population. As expected, nervous system tumors were disproportionately represented, and the relative frequencies of other tumors differed from expectations as well, especially under age 50. Multiple primary neoplasms were encountered in 16 members of the cohort, including five of the six patients with optic gliomas.

Other Interdisciplinary Studies. Collaborations for research on sister chromatid exchanges were used to establish a basis for greater epidemiologic use of this phenomenon, which has been a marker of population exposure to certain mutagens. Our program has repositories of cryopreserved lymphocytes, but most published experience is with fresh whole blood cultures. Therefore, a large experiment was designed to correlate spontaneous and mutagen-induced sister chromatid exchanges in fresh and frozen specimens from the same persons. Analysis showed that whole blood cultures had consistently lower levels than purified lymphocytes and that freezing lymphocytes for up to six months had no further effect.

Cytogenetic collaboration provided a suggestion of a new category of chromosomal disorders; namely, those associated with premature separation of centromeres. The phenomenon was seen in lymphocytes and fibroblasts from two sisters referred for evaluation because of melanoma in one and dysmorphologic syndrome in both. The syndrome proved to be the SC phocomelia syndrome with a new feature of congenital paralysis of three cranial nerves (seven, nine and ten).

Synthesis. An editorial, published in the New England Journal of Medicine, emphasized the ecogenetic origins of human cancer as illustrated by cancer families. A review of the cytogenetic abnormalities associated with human cancer revealed 11 chromosomes now associated with leukemia and 7 with solid tumors. Two human cancer genes can be assigned with confidence: retinoblastoma to 13q and Wilms' tumor to 11p. Four chapters on cancer genetics were published in the Proceedings of the International Workshop on Familial Cancer held in Basel, Switzerland. Two additional book chapters provided comprehensive reviews of genetic factors in lung cancer and the fetal alcohol syndrome. Thoughts on future research in occupational ecogenetics, neurofibromatosis, and the genetics of nasopharyngeal carcinoma were published in various conference Proceedings.

Resources. Six major contracts continued to provide nationally recognized laboratory expertise for our collaborations on cytogenetic and radiosensitivity mechanisms of carcinogenesis. (See contract narratives below).

Consultations, Committees, and Lectures. In an effort to recruit junior staff and to promote clinical and laboratory collaboration, teaching responsibilities were carried out in the NIH Interinstitute Medical Genetics Training Program, the Pediatric Branch of the National Cancer Institute, George Washington University School of Medicine, and the Uniformed Services University of the Health Sciences.

Consultation, in the form of committee membership, was given by Dr. Mulvihill to the Committee on Epidemiology of the International Commission for Protection Against Environmental Mutagens and Carcinogens, the U.S.-Japan Joint Panel on Environmental Mutagenesis and Carcinogenesis of the U.S.-Japan Cooperative Medical Science Program, and the Committee on Future Directions of the Environmental Mutagen Society.

Critical reviews of manuscripts were prepared for Johns Hopkins University Press, Blood, Cancer, Cancer Genetics and Cytogenetics, Genetic Epidemiology, Journal of the American Medical Association, Journal of the National Cancer Institute, and Teratology. Grant applications were critiqued for the Committee on Advanced Study and Research in China, The National Foundation-March of Dimes, the Netherlands Cancer Foundation and the Louisiana Cancer and Lung Trust Fund Board.

Publications:

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CONTRACTS IN SUPPORT OF THIS PROJECT

HEALTH RESEARCH INC., ROSWELL PARK MEMORIAL INSTITUTE (NO1-CP-21033)

Title: Genetic Factors in Patients at High Risk of Cancer--Tumor Chromosome Analysis.

Current Annual Level: $31,145

Person Years: 1.38

Objectives: To determine if tumors from persons with cancer have cytogenetic abnormalities which may ultimately be important in tumor etiology.

Major Contributions:

The laboratory has been sent 82 tumor specimens in the past year. Tumor types for which more than one specimen has been submitted include soft tissue sarcoma (22 cases), renal cell carcinoma (21), mesothelioma (13), breast cancer (12), osteosarcoma (3), benign neurofibromas (3), and testes cancer (2). One specimen was submitted for each of six other tumor types.

Studies of the soft tissue sarcomas revealed, for the first time, a tumor-specific translocation involving the X chromosome, t(X;18). To date, this change has been detected in this laboratory in seven synovial cell sarcomas, making this an etiologically relevant cytogenetic abnormality. This finding may help localize genes involved in the etiology of this tumor type. We plan to continue to submit large numbers of soft tissue sarcomas to see if a unique cytogenetic change can be found for each subtype.

Our interest in renal cell carcinoma stems from our finding in 1979 of a family with 10 cases of renal cancer and a translocation between chromosome 3 and 8 in all affected individuals. Because of this family, we submitted a series of sporadic cases of renal cell carcinoma to the contractor for study. The most frequently observed cytogenetic changes in these tumors involved the same region of the short arm of chromosome 3 in which the breakpoint occurred in the renal cancer family. This suggests that genes in this chromosome region may be important in the development of renal cancer.

The laboratory's data on mesothelioma, a tumor primarily caused by asbestos exposure, also indicate that the same region of 3p is the most common site of cytogenetic change in these tumors, although abnormalities in this region were not present in all of them.

HAZELTON BIOTECHNOLOGIES (formerly LITTON BIONETICS, INC.) (NO1-CP-21035)

Title: Genetic Factors in Patients at High Risk of Cancer--Sister Chromatid Exchange Analysis.

Current Annual Level: $0

Person Years: 1.61

Objectives:

To determine if lymphocytes and fibroblasts from persons with cancer, or at risk of cancer, have altered levels of either sister chromatid exchanges (SCE) or other types of cytogenetic abnormalities. Analysis is done in baseline studies, after exposure to chemical mutagens.

Major Contributions:

The laboratory has completed baseline and mutagen-induced sister chromatid exchange (SCE) analyses on cryopreserved lymphocytes from approximately 122 individuals. These specimens have been from patients with the dysplastic nevus syndrome (DNS) and melanoma, and their normal spouses who served as controls, affected and unaffected individuals with the nevoid basal cell carcinoma syndrome (NBCCS), affected and unaffected individuals who are members of a variety of sarcoma-breast cancer families, and affected and unaffected members from several families with lymphoproliferative malignancies including hairy cell leukemia and Hodgkin's disease. To date, no statistically significant abnormal SCE levels have been found in patients with either DNS or the NBCC syndrome. The results of the SCE studies on the other categories of patients have not yet been analyzed.

We have in press a manuscript on results from this contract evaluating the use of purified and cryopreserved lymphocytes for SCE analysis. In it, we report that purified lymphocytes had consistently and significantly higher baseline SCE frequencies than cells from whole blood cultures and were consistently more sensitive to two of the mutagens that we evaluated. Apart from this, we observed no consistent effect of freezing on baseline or induced SCE frequencies in the purified lymphocytes. This suggests that purification and cyro-preservation of human lymphocytes does not alter the baseline or mutagen-induced SCE responses and indicates that in certain epidemiological, occupational and monitoring situations, lymphocytes prepared in these ways may have logistical and technical advantages over the use of fresh blood.

UNIVERSITY OF CALIFORNIA AT LOS ANGELES (N01-CP-71081)

Title: Genetic Factors in Patients at High Risk of Cancer--Genetic Markers for Linkage Analysis (Assay A-Assays of Protein Polymorphisms).

Current Annual Level: $51,176

Person Years: .41

Objectives:

The major goal of this contract is to determine the chromosomal location of genes known to cause cancer in humans. Once the cancer (or disease) of

interest has been shown to result from a defect in a single gene, the function of the laboratory is to determine the genotypes of some 28-32 red blood cell enzymes, antigens and serum proteins with known chromosomal locations in affected and unaffected individuals from the families in which the gene of interest is segregating. These results are sent to NCI where they are analyzed in conjunction with the pedigree data to determine if there is any evidence of the disease gene being linked to any red blood cell or serum polymorphism.

Major Contributions:

This year the laboratory has received and processed blood and serum specimens from 130 persons. The following categories of specimens have been submitted:

Disorder	Number of Families	Number of Specimens
Hypertrophic cardiomyopathy	2	61
Waldenstrom's macroglobulinemia	3	36
Familial pheochromocytoma	2	16
Familial parathyroid carcinoma	1	10
Hypereosinophilia syndrome	1	7
Total	9	130

Preliminary analysis of the polymorphic markers in the hypertrophic cardiomyopathy families have suggested possible linkage of the gene for this disease to ACP1 (acid phosphatase) on chromosome 2p. DNA RFLPs from this chromosome are now being analyzed in members of these families to see if this linkage is confirmed.

The protein polymorphisms have not yet been analyzed in the remaining families.

This contract terminates 9/29/92.

INTEGRATED GENETICS, INC. (NO1-CP-71127)

Title: Genetic Factors in Patients at High Risk of Cancer--Genetic Markers for Linkage Analysis (Assay B-Assays of DNA Polymorphisms).

Current Annual Level: $236,887

Person Years: 1.6

Objectives:

The major goal of this contract is to determine the chromosomal location of genes known to cause cancer in humans. Because the work done under this contract is very labor intensive, in general, it is not used unless linkage analysis with the protein polymorphisms (Assay A above) either suggests a possible chromosomal location for a disease gene or is completely uninformative with respect to the location of a disease gene. In the first instance, RFLPs from the chromosome of interest are the first to be studied in DNA from the involved families. In the second scenario, DNA from the involved families is evaluated with a panel of probes representing each chromosome arm.

The data obtained from the RFLP analysis of DNA from families under study are then sent to NCI for the appropriate linkage analysis.

Major Contributions:

This year, the laboratory has received DNA from 65 members of a large family with multiple endocrine neoplasia type 1 (the autosomal dominant occurrence of parathyroid, pituitary and pancreatic tumors). After we embarked on this project, DNA studies of two insulinomas from patients with this disorder were done by another group which demonstrated loss of markers on chromosome 11. This suggested that the MEN1 gene might be on this chromosome, an inference that was confirmed through analysis of chromosome 11 RFLPs in their three families. We are now in the process of mapping the gene very precisely within 11q13 by using a variety of DNA probes flanking this chromosome region on DNA from several large MEN1 kindreds.

This contract terminates 9/30/1992.

DEPARTMENT OF ENERGY, BROOKHAVEN NATIONAL LABORATORY (Y01-CP-20518)

Title: In Vitro Radiosensitivity and DNA Repair in Genetic Syndromes and Families at High Risk of Malignancy

Current Annual Level: $310,950

Person Years: 3.2

Objectives:

To determine if persons with increased susceptibility to cancer, e.g., members of cancer families, individuals with multiple primary tumors, radiogenic tumors or genetic disorders predisposing to cancer, have abnormal repair of DNA damage induced by UV light, X-radiation or a variety of chemicals, and when repair defects are found, to identify the underlying cellular mechanisms.

Major Contributions:

New fibroblast strains sent to the laboratory in the past year have been from Israeli immigrants irradiated in childhood for ringworm of the scalp. The strains consist of two groups: those from persons who developed cancer (usually of the thyroid or brain) following radiation exposure, and those from persons who did not. These strains have been the major focus of the laboratory's recent work.

In order to evaluate possible differences in response to ionizing radiation of the Israeli strains, the laboratory has been trying to develop a method that will distinguish among the cell growth characteristics of strains from normal individuals, persons homozygous for ataxia-telangiectasia (AT), and persons who are heterozygous for AT. This is necessary because we have postulated that the Israelis who developed tumors as a result of the radiation exposure may in fact be AT heterozygotes (the AT gene is known to be present in high frequency in the North African population from which the Israeli immigrants came) and possibly have an increased predisposition to radiogenic malignancies as a result. AT is an autosomal recessive condition which predisposes to lymphoproliferative malignancies and, both in vivo and in vitro, has abnormal sensitivity to ionizing radiation. In vitro, the D_{10} values for ionizing radiation of AT homozygotes are significantly lower than for controls, so that the two groups can be distinguished. Although some scientists have reported that the D_{10} values of strains from AT heterozygotes are intermediate between those of the AT homozygotes and normal individuals, this has not been generally confirmed.

To date, the Brookhaven laboratory has used a variety of different methods to see if any will consistently differentiate AT heterozygotes from normal individuals: these have included x-ray treatment of exponentially growing cells, x-ray treatment of confluent cell cultures, treatment of cell cultures with chronic doses of x-rays and treatment with neocarzinostatin, a radiomimetic chemical. Although none of these approaches can consistently distinguish AT heterozygotes from normal individuals, the laboratory has made parallel studies with the Israeli strains, in case some differences appear among them.

The method currently being evaluated (the Cumulative Labelling Index) involves irradiating cells in stationary growth, subculturing them in H^3-containing medium and then observing the number of cells that begin to divide as measured by the incorporation of the H^3 into DNA. For unknown reasons, the fraction of cells in which the x-ray treatment permanently blocks growth is much higher in AT heterozygotes than in controls. The Brookhaven laboratory has been able to replicate these results. The Israeli strains have also been studied using this method, but we will not break the code to determine the tumor status of the donors of these strains until replicate experiments have been completed.

This interagency agreement terminates 9/27/89.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04400-23 CEB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Clinical Epidemiology of Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Frederick P. Li	Chief, Clinical Studies	CEB	NCI
Others:	R. W. Miller	Chief	CEB	NCI
	J. J. Mulvihill	Chief, Clinical Genetics	CEB	NCI
	D. M. Parry	Geneticist	CEB	NCI

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Clinical Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.8	2.0	0.8

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Persons who have an exceptionally high risk of developing cancer are studied to find explanations for their susceptibility. These unusual individuals are identified through referral by practitioners or self-referral and through clinical observations at the bedside. With informed consent, epidemiologic inquiries are made to identify predisposing host and environmental factors, and concurrent laboratory studies help to clarify biologic mechanisms of cancer susceptibility. Results show that carriers of cancer genes develop cancer at very high rates in a few tissues. Early cancer detection has been achieved through screening of high-risk persons, and counseling has been provided to appropriate patients. High-risk patients also tend to develop multiple primary cancers in childhood, and nearly 1000 patients are under prospective observation for second cancers through the Registry of Survivors of Childhood Cancer in Boston. An additional series of nearly 2,000 survivors of childhood retinoblastoma in New York and Boston are being registered for long-term follow-up.

groups have shown chromosome 3p rearrangements in renal cancer tissues of non-familial cases, suggesting its importance to the development of this neoplasm. Several polymorphic fragments (D1S1,D3S2, and D3S3) have been mapped to the region 3p14-21, and these and other polymorphic probes are being used to further localize the breakpoint on chromosome 3 in our family. The hypothesis is that the gene on 3p that is involved in the development of human renal carcinoma is at the breakpoint of the t(3;8) in this family.

The Familial Breast Cancer-Sarcoma Syndrome

Since initial identification of this syndrome in 1969, additional affected families have been ascertained by members of the Branch. An analysis of 24 of these families has clarified the clinical features of the disorder. The inheritance pattern is autosomal dominant, with cancer expressed by 45 years of age in most family members. The tumor types present in these families include sarcomas of bone and soft tissue, acute leukemia, brain tumor, adrenocortical carcinoma and breast cancer. Investigations are in progress of 13 additional families that appear to have this syndrome. Laboratory studies of affected family members have started to reveal insights into the pathogenesis of this syndrome. Cytogenetic studies of soft tissue sarcomas from familial and sporadic cases show correlations between chromosomal translocation and histological subtype of the sarcoma. These include the translocation, t(X;18), in synovial sarcoma, deletion of chromosome 11p in rhabdomyosarcoma and translocation between chromosomes 12 and 16 in liposarcoma. The findings may be useful in classifying poorly differentiated soft tissue sarcomas, and to localize genes involved in the development of sarcomas. In addition, studies of the recessive oncogene Rb1 (from human retinoblastoma) has shown homozygous deletions in 3 of 16 soft tissue sarcomas.

Mesothelioma in Cigarette Filter Makers

We recently observed mesothelioma in three men who had made cigarette filters which contain asbestos. All had worked for one small company between 1951-1958. According to the patient, the cigarette filter contains 5 to 30 percent blue asbestos, or crocidolite. An additional 35 workers at this plant have been identified and five cases of mesothelioma, 7 lung cancers, and 4 of fatal asbestosis were found.

Delineation of New Cancer Susceptibility Syndromes

Work is in progress to identify new cancer susceptibility syndromes and variants of previously recognized syndromes. In studies of dominantly transmitted polyposis coli, four families were found in which a child has developed hepatoblastoma. This association was first described in England several years ago. In Boston, one child with hepatoblastoma has survived the liver tumor for 5 years. When the association between hepatoblastoma and polyposis was recognized, the child underwent colonoscopy with the finding of early polyps. Three additional members of her family were also found to have previously unrecognized polyposis

Project Description

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

F. P. Li	Chief, Clinical Studies	CEB	NCI
R. W. Miller	Branch Chief	CEB	NCI
J. J. Mulvihill	Chief, Clinical Genetics	CEB	NCI
D. M. Parry	Geneticist	CEB	NCI

Objectives:

To employ clinical observations at the bedside to find causes of human cancers. Susceptibility factors in the development of cancer are identified and high risk subgroups in the population are examined with new laboratory techniques to uncover biologic mechanisms of predisposition to cancer. In addition, counseling and consultation regarding appropriate medical management are provided to these cancer-prone persons.

Methods Employed:

Patients admitted for cancer therapy at the Dana-Farber Cancer Institute are examined for clues to the etiology of the neoplasm. When exceptional clinical observations are made, appropriate follow-up epidemiologic and laboratory investigations are conducted. In the past year, several striking family aggregates of specific cancers have been identified. Family members are under study to identify reasons for the susceptibility and to detect early cancers. In addition, a registry has been established at the Dana-Farber Cancer Institute of nearly 1000 patients who have survived childhood cancer for at least five years and 2000 retinoblastoma patients treated in New York and Boston. These patients are being studied to determine the probability of development of a new cancer and the somatic and genetic effects of the neoplasm in childhood. Prospective studies are in progress to confirm predictions of high risk of cancers in individuals, families, and other groups. Collaboration has been established with basic scientists at the Dana-Farber Cancer Institute to conduct studies on tumor specimens--mesotheliomas, sarcomas and renal cancers--for studies of chromosome and molecular changes in tumor cells.

Major Findings:

Hereditary Cancers of the Genitourinary Organs

Additional studies continue to be made of a family with 10 cases of renal cancer and a translocation between chromosomes 3 and 8. Somatic cell hybrids with the derivative chromosomes show that the c-myc oncogene on chromosome 8q24 was translocated to the derivative 3 and that the restriction fragment length polymorphism (RFLP), D3S2, is rearranged to the derivative 8. However, pulse field gels show that c-myc is not within 700 Kb of the breakpoint. Studies of chromosome 3 by several

coli and have undergone colectomy. We have now established a Registry of the Hepatoblastoma-Polyposis Coli Association and collection of specimens for laboratory studies have begun.

In a patient with the newly described syndrome, cystic hamartomas of the lung, a uterine stromal sarcoma developed which showed insertion of chromosome 19 into chromosome 10.

We have recently observed five cases of multiple primary cancer that include melanoma and soft tissue sarcoma. Two of them also have dysplastic nevus syndrome (DNS). The possibility that sarcomas are a previously unrecognized feature of DNS is under study.

Late Effects in Survivors of Childhood Cancer

A number of studies have been undertaken to evaluate adverse effects of late onset. In a 10-year prospective study of second cancers at the Dana-Farber Cancer Institute, 30 new cancers were observed when two were expected. All but two of the second cancers were solid tumors. The tumors usually occurred within the field of radiation therapy. The analysis is now being extended to 15 years of prospective follow-up.

A seven-hospital study was made of pregnancy outcome in patients treated in childhood for Wilms' tumor. The data show a high frequency of adverse pregnancy outcome in women who had received abdominal radiation therapy for the neoplasm. Among these patients, the rate of adverse pregnancy outcome was 30%, a rate eightfold above expectation. The adverse outcome included excess neonatal and perinatal mortality and the birth of low-weight infants. These abnormalities were not present in female patients who had not received abdominal radiation. To pursue this unexpected observation, a new series is being gathered of offspring of patients who survived cancers other than Wilms' tumor. The hypothesis is that low birth weight will be observed among offspring of irradiated female patients.

A recent study reported a 90% risk of second cancers, primarily sarcomas, among nearly 800 survivors of hereditary retinoblastoma. However, the risk estimate may be flawed by a high proportion of cases lost to follow-up. To refine the risk, a follow-up study of these cases and 1200 others with retinoblastoma is in progress. The study has provided access to tissues of second cancer in retinoblastoma patients. These tissues will be probed with the newly cloned retinoblastoma gene to study the role of this gene in secondary neoplasms.

The frequency of hypertension has been studied in a series of Wilms' tumor patients who had nephrectomy and other treatments between 14 and 53 years ago. Eighty percent are normotensive. The overall frequency of hypertension did not exceed expectation based on data for the general population. The data provide assurance that hypertension is not a common sequelae of treatment for Wilms' tumor.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05139-09 CEB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

NIH Interinstitute Medical Genetics Program: The Genetics Clinic

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Dilys M. Parry	Geneticist	CEB	NCI
Others:	J. J. Mulvihill	Chief, Clinical Genetics Section	CEB	NCI
	C. A. Collins	Research Assistant	CEB	NCI

COOPERATING UNITS *(if any)*

CC (S. Schlesinger); NEI (M. Kaiser-Kupfer); NIADDK (D. Camerini-Otero, B. White); NICHD (W. Gahl, J. Sidbury, M. Zasloff); NIDR (K. Brown, C. Hughes); NINCDS (R. Eldridge, N. Barton)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Clinical Genetics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	1.7	1.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Genetics Clinic is a collaborative undertaking by researchers from six NIH institutes and the NIH Clinical Center. Consequently, clinic patients constitute a broad spectrum of genetic disease. The patient load during the clinic's seventh year comprised 278 individuals representing some 60 different diagnostic categories. Of these, 109 patients (39%) were seen by members of the Clinical Epidemiology Branch (CEB). For our Branch, the Clinic provides a multidisciplinary setting in which to study unusual patients who either have cancer or an increased risk of developing malignancy. Patients are ascertained through special referrals from outside physicians and from inhouse requests for etiologic consultations. With informed consent, the approach to the patient includes detailed physical examination and, where applicable, epidemiologic studies of the environmental and genetic background and laboratory studies to clarify biologic mechanisms of carcinogenesis. Categories include patients with genetic diseases predisposing to malignant or benign neoplasms, patients with birth defects and cancer, families with childhood sarcomas and breast cancer in blood relatives, and any other families with an excessive occurrence of cancer of any type.

Project Description

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

D. M. Parry	Geneticist	CEB	NCI
J. J. Mulvihill	Chief, Clinical Genetics Section	CEB	NCI
C. A. Collins	Research Assistant	CEB	NCI

Objectives:

1. To provide a multidisciplinary setting in which patients with cancer or at high risk of developing cancer can be studied through clinical and laboratory collaboration to identify host or environmental factors for increased cancer risk.

2. To provide counseling for persons at high risk of malignancy and recommend appropriate medical surveillance for the early detection of tumors.

3. To provide training to graduate physicians and medical students in the diagnosis, counseling, and treatment of individuals with, or at risk of, genetic disease, and in the research approach to genetic disease.

Methods Employed:

Referred patients are examined to determine the extent of any pre-existing condition or birth defects and for clues to the etiology of cancer in themselves or family members. When exceptional clinical observations are made, appropriate follow-up epidemiologic and laboratory investigations are conducted. For research studies, specified categories of patients are examined and tested according to an established protocol to ensure uniform data collection. Physicians and medical students in training undertake patient interviews, physical examinations, and treatment and counseling under the direct supervision of an attending physician.

Clinic Patients Seen by Members of the Clinical Epidemiology Branch

Bilateral acoustic neurofibromatosis (NF2)	30
von Recklinghausen's neurofibromatosis	21
Familial pheochromocytoma	18
Women at high risk of breast cancer	8
Familial hypereosinophilia syndrome	5
Down's syndrome	4
Familial acute myelogenous leukemia	2
Cowden's disease	1
Multiple skin cancers	1
Ataxia-telangiectasia	1
Multiple endocrine neoplasia type 1	1
Total	92
Birth defect or familial syndromes	17
Grand total	109

Major Findings:

1. We continue to be interested in clarifying the genetics and natural history of von Recklinghausen's neurofibromatosis (NF1). Using DNA from several of our families, Dr. Bernd Seizinger, Massachusetts General Hospital, determined that the gene for NF1 is located near the nerve factor receptor gene on the long arm of chromosome 17. Confirmation of the gene being on chromosome 17 came from researchers in Salt Lake City. The localization of the NF1 gene has profound implications for both basic research and clinical practice and greatly increases the likelihood of determining the primary defect in this disorder. Since the ability to correlate clinical manifestations with changes at the level of DNA will soon be realized, we intend to continue evaluating families with this disorder, especially those with "extreme" clinical manifestations; that is, families that overall are very mildly or very severely affected.

Among the NF1 patients that we saw this year, two were from particularly interesting families. One patient, a 22-year-old woman, was from a family whose DNA was used in the genetic linkage studies. Based on the DNA markers, she should have had NF1, but our clinic notes from 8 years ago stated that she was unaffected. Thus, she was potentially a recombinant; this would make her family especially useful for future gene mapping studies. In order to confirm her clinical status, we brought her to NIH. Based on a thorough clinical evaluation, she had no evidence of NF1, and thus was a true recombinant. DNA from this family is now being used to map NF1 with respect to centromere markers on chromosome 17.

The second NF1 family of special interest was unusual because of the very mild clinical manifestations in two family members. The proband was a 9-year-old girl who had sufficient criteria to be diagnosed unequivocally, e.g., more than 5 cafe-au-lait spots and Lisch nodules in both irises. She was the only known case in her family. Since NF1 is an autosomal dominant disorder, her parents were very carefully examined to make sure that neither one had the NF1 gene without any obvious manifestations of it. Her mother had no evidence of NF1, but her father had one feature--Lisch nodules in both eyes. These are rarely seen in the absence of this gene. Fortuitously, he had an identical twin who agreed to come to the clinic. To our surprise, the twin also had Lisch nodules without any other features of NF1. The findings in these twins demonstrate the need for very careful clinical examination of members of NF1 families, especially since genetic counselling is dependent on the clinical findings.

2. During the past year, Drs. Parry and Mulvihill have expanded their interest in the neurofibromatoses to include bilateral acoustic neurofibromatosis (NF2), an autosomal dominant condition genetically distinct from NF1. This disorder causes the development of schwannomas of the vestibular nerve, usually resulting in bilateral hearing loss in adolescent or early adult life. Surgical removal of these tumors presents formidable difficulties because of the risks of facial and auditory nerve damage. This condition is also associated with a high incidence of meningiomas, gliomas and neurofibromas of the spinal nerve roots. Presenile

lens opacities or cataracts have been detected in about half of evaluated patients with NF2. DNA studies of tissue from acoustic neuromas and meningiomas from NF2 patients and from blood from a three generation NF2 family have indicated that the gene for this disorder is on chromosome 22. In an attempt to confirm the chromosome 22 linkage, and to evaluate the efficacy of ophthalmologic, audiologic and magnetic resonance imaging in identifying presymptomatic carriers of the NF2 gene, we have studied an NF2 kindred that was last seen 14 years ago. Blood for restriction fragment length polymorphism (RFLP) analysis was obtained from 41 members of this family and 23 people were brought to NIH for clinical evaluation.

We diagnosed acoustic neuromas in five persons not previously known to have tumors. The four youngest (mean age 24.8 years) had no hearing loss, whereas the oldest, a 70-year-old man, had a progressive hearing loss of about 20 years duration. Six others had been diagnosed previously with acoustic neuromas; one was totally deaf and had facial diplegia and four others were deaf in one ear following surgical intervention; the latter had profound hearing loss in the remaining ear from untreated tumor. Ten of the 11 people with acoustic neuromas had ophthalmologic exams; posterior lens opacities or cataracts of early onset were present in seven; the three without posterior lens changes were young (ages 21, 25 and 27), so lens changes may yet develop. Clearly, the imaging and eye exams have been useful in identifying family members with asymptomatic tumors; however, because the development of lens changes and tumors are age-dependent, identification of even younger gene carriers may require the DNA studies which have not yet been completed in this family.

3. Mental retardation and small head size are recognized sequelae of in utero exposure to ionizing radiation, especially during the third to 20th week of gestation. Childhood cancer has been linked to diagnostic exposure to radiation anytime during gestation but not to gestational radiotherapy. Last year, we evaluated a man who had volunteered to be studied because he had survived in utero exposure to massive radiation 47 years earlier. As verified by hospital records, he had received 3 days of ionizing radiation (estimated to have been 180-300 rads to the brain, 40-50 rads to mid-trunk and 15 rads to the gonads) during the third trimester from the radium implanted into his mother's vagina to treat her cervical carcinoma. Our examination showed he had mild relative microcephaly (but no mental retardation) and a possible diagnosis of multiple sclerosis, but no other ill effects. His peripheral lymphocytes showed no elevation of chromosome or chromatid aberrations relative to a normal control. Interestingly, he had a grandson with Down's syndrome as a result of trisomy 21 and he specifically asked whether the radiation exposure he received could have caused one of his chromosome 21s to have behaved abnormally and thus be present in an extra dose in his grandson. To address this question, peripheral blood for chromosome studies was obtained from our proband (the grandfather), his daughter and son-in-law, and the infant with Down's syndrome. The paternal grandmother was not available.

Karyotype analysis confirmed a normal chromosome number in all except the infant with Down's syndrome who was 47 XY +21. Quinacrine and silver

staining patterns of this child's three number 21 chromosomes showed that each had a different short arm polymorphism, indicating an error in chromosome disjunction during metaphase of meiosis I. However, since both parents had one polymorphism of chromosome 21 that was identical, the origin of the nondisjunction, that is whether it occurred during meiosis in the mother or the father, could not be determined. Thus, no conclusion could be made concerning the involvement of a chromosome 21 from the child's maternal grandfather.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05146-09 CEB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Morbidity in Childhood Cancer Survivors and Their Offspring

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	John J. Mulvihill	Chief, Clinical Genetics Section	CEB		NCI
Others:	J. M. Byrne	Epidemiologist		CEB	NCI
	R. R. Connelly	Statistician		DCPC	NCI
	M. H. Gail	Head, Epidemiologic Methods	BB	DCE	NCI
	T. R. Fears	Statistician	BB	DCE	NCI

COOPERATING UNITS *(if any)*

NICHD, Bethesda, MD (R. Sherins); University of Minnesota, Minneapolis, MN (L. Robison); NICHD, Bethesda, MD (J. Mills)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Clinical Genetics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.1	2.0	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Fertility and reproductive histories of cancer patients, especially of long-term survivors of childhood and adolescent cancer, and of men and women who reproduced during cancer therapy, are studied for information on the gonadal toxicity and possible mutagenicity and teratogenicity of cancer treatment, and also to uncover hereditary patterns of cancer. Current phases include intensive analysis of data from interviews and medical records of 2498 cancer survivors and their 3604 sibling controls to learn about their subsequent health and fertility and the health of their offspring. In 7117 offspring, 18 cancers occurred--not a significant excess over expected numbers. Survivors of childhood brain tumors were less likely to complete 8th grade, or to enter college after high school graduation.

Both male and female survivors reported 30% fewer pregnancies than controls; treatment with combined radiation and alkylating agents depressed fertility in survivors to only one-third that of controls. A second phase is a voluntary registry of pregnancies in women with cancer. Preliminary results suggest no excess of birth defects, but some excess wastage of pregnancies conceived within 12 months of completing chemotherapy. An International Conference on Reproduction and Human Cancer was held in May 1987, and its Proceedings are in preparation. Additional studies at the NIH Clinical Center and a multinational study group are in development. Follow-up studies of former leukemia patients are planned, in collaboration with the Childrens Cancer Study Group and the National Institute of Child Health and Human Development.

Project Description

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

J. J. Mulvihill	Chief, Clinical Genetics Sect.	CEB, NCI
J. M. Byrne	Epidemiologist	CEB, NCI
R. R. Connelly	Statistician	SORB, DCPC, NCI
M. H. Gail	Head, Epidemiologic Methods Sect.	DCPC, NCI
D. M. Parry	Geneticist	DCPC, NCI
E. Mostow	Staff Fellow	CEB, NCI
R. Haupt	Visiting Scientist	CEB, NCI

Objectives:

To document fertility and reproductive outcome in patients who become pregnant before, during and after cancer treatment. The goals are to test genetic theories of cancer etiology; to define potential gonadal toxicity of cancer treatment, both teratogenicity and mutagenicity; and to provide needed information for genetic counselling of long-term cancer survivors. The hypothesis being tested is that cancer patients have excessive morbidity due to additional malignancies, or other illnesses and impaired reproductive performance, including an increased frequency of offspring with birth defects or cancer.

Methods Employed and Major Findings:

The Five Center Study. Intensive interviewing and record abstraction in five collaborating centers are complete in 2498 individuals who had cancer under age 19 years, survived at least 5 years and reached age 21 years. The 3604 controls, chosen from among the siblings of the survivors, were also studied for subsequent morbidity, mortality, quality of life, fertility and health of offspring. Intense analysis is underway. Marriage rates in our survivors were significantly less than in controls; males had a 30% marriage deficit compared to male controls, while females were not different from female controls in their marriage rates. Most of the male marriage deficit occurred to survivors of brain and central nervous tumors, who were 30% less likely than their controls to marry. Income deficits were also seen in male cancer survivors, again among brain tumor survivors principally. We speculate that the same cognitive and functional problems attendant upon treatment for brain tumors which lead to income deficits also make them poor marriage prospects.

Married survivors, both male and female, were 30% less likely than controls to have reported a pregnancy by the end of the follow-up period. Surgical treatment, radiotherapy and chemotherapy with alkylating agents had increasingly severe effects on fertility. Combined radiotherapy and treatment with alkylating agents had the worst prognosis--survivors treated with the combined therapy had only one-third the fertility rates of their sibling controls. Female fertility was relatively unaffected by alkylating agent therapy alone, in contrast to males, who were severely

affected. In collaboration with Dr. Mitchell Gail of the NCI BIostatistics Branch, we are investigating the rates of menopause in female survivors compared to female controls. At the time of interview, 22% of survivors were post-menopausal compared to 15% controls. The average age at menopause for survivors was 25 versus 35 for controls. All cancer treatments were associated with early menopause in the period shortly after the start of therapy, but only two--radiation below the diaphragm alone and radiation below the diaphragm plus alkylating agent chemotherapy--were associated with effects lasting more than 10 years since the start of treatment.

An analysis of educational attainment showed that survivors of most tumor types had the same achievement as controls, but those with tumors of the brain and central nervous systems were less likely than controls to have completed 8 years of school or to have entered college.

In a paper submitted for publication, data from the Five-Center Study confirm a previous report that female survivors of Wilms' tumor who were treated with abdominal radiation have more trouble successfully completing a pregnancy, i.e., more low birth weight babies and more preterm deliveries. These women also have more children with birth defects than female controls. Male survivors reported no such problems in their wives. After noticing that 22% of our survivors denied having cancer, we investigated possible explanations for this. We found that survivors who were treated in earlier decades, who were nonwhite, who came from Connecticut or who were treated with surgery alone were less likely to know their cancer diagnosis. Survivors of malignant and nonmalignant brain tumors almost all denied having cancer, but when queried about "benign tumor" reported that they had had a "brain tumor." We analysed rates of birth defects in offspring of survivors compared to offspring of controls. Using various sources of ascertainment--parents' reporting, cancer registry records and other medical records--no association between parents' history of cancer and offsprings' birth defects could be detected. When we looked at the subgroup of survivors exposed to mutagenic or teratogenic therapy, compared to offspring of survivors not so exposed, there was no excess of birth defects.

We compared the rates of cancer in the offspring with age-adjusted rates from the general population, and with rates in nieces and nephews of survivors. The observed numbers were not significantly different from those expected in the general population. The study had an overall power of 79% to detect a threefold excess of cancer among survivors' offspring. An excess was not detected.

In our analyses to date we have not detected any evidence that potentially mutagenic cancer therapy is actually linked to genetic effects in the offspring. Other endpoints (e.g., sex ratio and fetal loss) are being studied.

Other Collaborations. A report concerning 133 pregnancies in 66 young women with cancer, assembled from physicians participating in Cancer and Acute Leukemia Group B was published. The analysis showed little, if any, teratologic effect, but some excess wastage of pregnancies conceived within 12 months of completing chemotherapy. A preliminary report was made of

a special registry of pregnancies underway during cancer therapy. A draft protocol is being circulated to collect further data on outcomes of pregnancies in and by cancer patients in Europe.

Through a collaborative arrangement with the Children's Cancer Study Group, we are exploring the possibility of studying various aspects--late effects of leukemia and its treatment in long-term survivors. We plan to do an interview study of survivors over 18, similar to the Five-Center Study, to examine the health and fertility of survivors and the health of their offspring. Two prospective clinical studies of growth and development are planned in collaboration with endocrinologists from National Institute of Child Health and Human Development and New York University. We plan to obtain tissue samples prospectively to look for precursors of future cancer development in these high risk children.

Plans are well underway for a follow-up study of cancer survivors treated at the NIH Clinical Center and their offspring conceived since treatment. The goal is to study at least three members of a family--the exposed survivors, the unexposed spouse and the offspring--for the possible mutagenic effects of treatment, manifested as mutant problems which may or may not have clinical significance.

Through a contractual arrangement set up by the Viral Epidemiology Section of NCI's Environmental Epidemiology Branch, we are collaborating with Dr. Janet Neequaye of the University of Ghana Medical School to study the fertility of long-term survivors of African Burkitt's lymphoma. Data collection has concluded, and we expect that analysis will commence in the summer of 1988.

Publications:

Byrne J. The impact of selected psychosocial factors on the reproductive choices of long-term survivors of childhood and adolescent cancer. In: Mulvihill JJ, Sherins R. eds. Reproduction and human cancer. New York: Raven Press. (In Press)

Byrne J, Mulvihill JJ, Connelly RC, Myers MH, Austin DF, Holmes GF, Holmes FF, Latourette HB, Meigs JW, Strong LC. Reproductive problems and birth defects in survivors of Wilms' tumor and their relatives. Med Pediatr Oncol (In Press)

Byrne J, Mulvihill JJ, Myers MH, Connelly RR, Naughton MD, Krauss MR, Steinhorn SC, Hassinger DD, Austin DF, Bragg K, Holmes FF, Latourette HB, Weyer PJ, Meigs JW, Teta MJ, Strong LC. Effects of treatment on fertility in long-term survivors of childhood and adolescent cancer. N Engl J Med 1987;317:315-21.

Byrne J, Mulvihill JJ, Myers MH, Kalish R, Connelly RR, Austin DF, Holmes FF, Holmes GF, Latourette HB, Meigs JW, Teta MJ, Strong LC. Marriage, fertility and premature menopause in survivors of childhood and adolescent cancer. Proc Am Soc Clin Oncol 1987;6:228.

Byrne J, Warburton D. Fetal and embryonic characteristics of monosomy X in spontaneous abortions. Ped Path 1987;7:480.

Canki N, Warburton D, Byrne J. Morphological characteristics of monosomy X in spontaneous abortions. Ann Genet 1987;31:4-13.

Kelaghan J, Myers MH, Mulvhill JJ, Byrne J, Connelly RR, Steinhorn SC, et al. Educational achievement of long-time survivors of childhood and adolescent cancer. Med Pediatr Oncol. (In Press)

Mulvihill JJ, Myers MH, Connelly RR, Byrne J, Austin DF, Bragg K, Cook JW, Hassinger DD, Holmes FF, Holmes GF, Krauss MR, Latourette HB, Meigs JW, Naughton MD, Steinhorn SC, Strong LC, Teta MJ, Weyer PJ. Cancer in offspring of long-time survivors of childhood and adolescent cancer. Lancet 1987;ii:813-7.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05194-07 CEB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less--Title must fit on one line between the borders.)*

National Cancer Mortality Studies by Computer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Robert W. Miller	Chief	CEB	NCI
Others:	F. W. McKay	Computer Systems Analyst	CEB	NCI
	P. Madigan	Research Assistant	CEB	NCI
	J. Byrne	Visiting Associate	CEB	NCI

COOPERATING UNITS *(if any)*

National Center for Health Statistics, Hyatttsville, MD (C. M. Croner)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.4	2.3	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have used information from the National Center for Health Statistics (NCHS) and Bureau of the Census to create a comprehensive data base concerning mortality and population information at the county level. Data are available, 1950-1981, for cancer mortality, and 1965-78, for deaths from other causes. Population data will be extended and corrected when the 1980 census data become available. Three-dimensional graphs employing these data are one example of the value of the data collection. Under development are systems for mapping counties in black-and-white, for projecting cancer mortality in coming decades, and for grouping counties by economic subregions.

Project Description

Name, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

R. W. Miller	Chief	CEB	NCI
F. W. McKay	Computer Systems Analyst	CEB	NCI
R. E. Tarone	Biostatistician	BB,DCE	NCI
P. Madigan	Research Assistant	CEB	NCI
J. Byrne	Visiting Associate	CEB	NCI

Objectives:

1. To develop new ways for evaluating existing cancer mortality data for the United States by computer.

2. To provide special data tabulations to others on request.

Methods Employed:

The cancer mortality data, which were collected by the National Center for Health Statistics (NCHS) for 1950-1982, have been worked into a data base which allows for selection by 4-digit International Classification of Diseases code and 18 age groups at the county level. Programs have now been developed on the IBM personal computer for creating three-dimensional graphs of cancer mortality rates by site, sex, calendar year and age-group, for whites and nonwhites.

A more economical use of computer time has been achieved through the use of programs written on the IBM personal computer.

1. Economic subregions and areas defined by the Bureau of Economic Analysis are being used to map type-specific cancers to determine high-risk areas. High rates of nasopharyngeal carcinoma have been observed along the Gulf Coast where economic subgroups were studied. A case-control study may reveal the reason for this geographic (socioeconomic?) peculiarity.

2. Variability in the high-risk areas obtained when different years are used as the standard for age-adjustment are under study by Mr. Frank McKay, assisted by Dr. Robert E. Tarone of the Biostatistics Branch.

3. Mortality is to be studied according to birth-cohorts.

4. Computer graphics techniques have been utilized to generate graphs of observed and expected numbers of deaths due to cancers of individual sites and groupings of sites, which are grouped based on whether or not there is a known association with smoking.

5. A "multiple cause of death" data system has been established. "Secondary" causes of death listed on death certificates can be selected along with underlying cause.

Major Findings:

1. A computer program was developed to match county population profiles by total population, and age and race distribution. This can be used to compare rates of cancer mortality in counties with similar demographic characteristics.

2. An analysis of cancer mortality in the 15 counties within the "Reading Prong" was made in an attempt to detect the effect (or lack thereof) of exposure to naturally occurring radon gas. Standardized mortality ratios were prepared using non-radon counties with similar populations as controls. Various combinations of control counties have been used thus far, and the computer program is currently being modified to use all of the U.S., other than the 15 radon counties, as the standard. The 11 cancer sites identified in the appendix to "Cancer Mortality and Radioactive Fallout in Southwestern Utah," plus all malignancies combined, are being used in the analysis. Bureau of the Census population estimates for 1960, 1970 and 1980 are being used with the mortality data, which are grouped for the years 1950-1964, 1965-1974 and 1975-1982. Preliminary results indicate an excess of nasopharyngeal cancer in the Reading Prong counties.

3. The U.S. Nuclear Regulatory Commission provided the Branch with a document that gives the location (and operational history) of the 98 reactors currently producing power in the U.S. Necessary data bases are being prepared, control counties selected and computer programs mediated, so that we may examine cancer mortality in the reactor-containing counties (and perhaps the counties down-wind) using techniques very similar to those being developed in the radon study.

4. Methodology previously used to analyze mortality data at the county, state economic area, economic subregion, and state is problematic. The county analysis has been particularly disturbing since different maps could be created from the same mortality data just by changing the population used as a standard. Mr. McKay discovered that the Bureau of the Census really does count people where they find them at census time. Military installations, universities and colleges, including junior colleges, and what appear to be correctional institutions cause some of the more serious distortions in the various counties. The problem is not insignificant--an estimated 10 to 20% of the counties in the coterminous U.S. are in the "odd population" category. The work that Ms. Patricia Madigan (CEB) and Mr. McKay did to develop computer programs to carefully match county population distributions for the purpose of selecting control counties for the radon study has been helpful in identifying the "odd" counties. Three-dimensional drawings of the population distribution of many counties are available as an effective way of illustrating the problem.

5. About 12 years ago, a committee was formed at the NCHS to examine ways of preparing and using maps for their data. To demonstrate feasibility, Mr. McKay has supplied an NCHS geographer with "Automaps," an exhibition of about 75 maps of the distribution of a broad range of mortality causes by economic subregions. The data cover 10 years, 1969-1978, encode diseases

to the 8th revision of the International Classification of Diseases. The maps, which show the significance of age-, sex-, and race-adjusted proportionate mortality rates for 19 sub-regions, can be viewed on any IBM-compatible personal computer equipped with a color monitor.

6. Dr. Charles Brown and Mr. Roger Connelly of the Division of Cancer Prevention and Control, NCI, are preparing a method for the more accurate and meaningful analysis of mortality rates of birth cohorts. Dr. Brown and Mr. McKay have prepared the necessary population data base (single year of age for ages 1-84, male, female, white and nonwhite) for each year since 1950. The same specifications are being applied to causes of deaths.

Publications:

Devesa SS, Silverman DT, Young JL, Jr, Pollack ES, Brown CC, Horm JW, Percy CL, Myers MH, McKay FW, Fraumeni JF, Jr. Cancer incidence and mortality trends among whites in the United States, 1947-84. JNCI 1987;79:701-70.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05279-06 CEB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Development of Epidemiologic Data Resource

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	G. W. Beebe	Statistician (Health)	CEB	E&B	NCI
Others:	M. Alavanja	Special Assistant	OAD	E&B	NCI
	A. E. Blair	Epidemiologist	EEB	E&B	NCI
	W. J. Blot	Chief	BB	E&B	NCI
	J. D. Boice	Chief	REB	E&B	NCI
	B. F. Hankey	Biostatistician		DCPC	NCI
	R. H. Hoover	Chief	EEB	E&B	NCI
	Z. Hrubec	Expert	REB	E&B	NCI
	R. Spirtas	Biostatistician	EEB	E&B	NCI

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.2	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

To facilitate the development of data resources for cancer epidemiology, a working group was established by the Director, NCI, in 1978. The membership includes those named above, with Dr. Beebe as chairman. The present functions of the group include creating a national data base for occupational mortality, reviewing Master Order Agreement-Requests for Proposals, oversight of the Veterans Administration (VA) hospital discharge file, liaison with National Center for Health Statistics in regard to the National Death Index, improving access to Federal record systems, and pursuing new leads. A number of contracts or interagency agreements have been initiated in support of this program, especially with the Social Security Administration (SSA), the Internal Revenue Service (IRS), and the National Institute for Occupational Safety and Health (NIOSH). A legislative initiative has been drafted in the Office of the Assistant Secretary for Health to widen the access of medical investigators to the address file of the IRS and to transfer IRS information on occupation of taxpayers to SSA. The number of states performing acceptable coding of occupation and industry increased to 18 for 1986.

Project Description

Names, Title, Laboratory and Institute Affiliating of Professional Personnel Engaged on this project:

G. W. Beebe	Health Statistician	CEB	E&B	NCI
M. Alavanja	Special Assistant	OAD	E&B	NCI
A. E. Blair	Epidemiologist	EEB	E&B	NCI
W. J. Blot	Chief	BB	E&B	NCI
J. D. Boice	Chief	REB	E&B	NCI
B. F. Hankey	Biostatistician		DCPC	NCI
R. H. Hoover	Chief	EEB	E&B	NCI
Z. Hrubec	Expert	REB	E&B	NCI
R. Spirtas	Biostatistician	EEB	E&B	NCI

Objectives:

1. To develop and facilitate access to data files likely to be useful for epidemiologic research.

2. To encourage the linkage of large administrative data files in the interests of epidemiologic research.

3. To oversee exploitation of the VA hospital discharge file.

Methods Employed:

Experiments are designed to test the technical feasibility and scientific adequacy of proposals for making use of data files in research on cancer and for linking large data files to produce new information. Methods used in other countries with more advanced data systems are studied for their possible usefulness in the United States. Legislative changes are sought in the interests of epidemiologic research.

Major Findings:

1. Work continues with the Internal Revenue Service (IRS) to determine if the occupational entries on the Form 1040 can be used effectively to update the Continuous Work History Sample (CWHS) maintained by the Social Security Administration (SSA).

2. The usefulness of SSA information on employment histories is being tested. The SSA has provided the histories of 200 men for comparison with parallel data obtained by interviews with the next-of-kin in a case-control study of mesothelioma.

3. Under an interagency agreement, SSA is obtaining death certificates and cause of death on CWHS subjects as a way of probing for differentials in mortality rates that may provide clues to carcinogenic hazards in the workplace. If successful, it should lead to a retroactive completion of data to 1968 and a forward projection after 1977. The United States would then have a national sample with which at least the major industries could be screened for carcinogenic hazards. High risks could be made the subject of specifically designed epidemiologic studies. This work will also create public use tapes enabling epidemiologists to use working population controls in lieu of general population controls in studies where the "healthy worker effect" hinders mortality comparisons.

4. Through the NCI-NIOSH cooperative program, NCI is funding the development of a national system of occupational mortality information by encouraging the states to code the information on death certificates and preparing NCHS to incorporate this information into the national vital statistics program. At a January 1987 Workshop on Occupational Mortality organized by NCHS, the Bureau of Labor Statistics, and the National Institute for Occupational Safety and Health, NCHS representatives were not hopeful that this developmental work could continue beyond FY 88 unless NCI funding was continued beyond that year, despite the interest expressed by State registrars and representatives of other agencies. However, NCI has communicated to CDC the importance of this program and has encouraged them to take an active role during the budget process so that NIOSH and NCHS can further the program.

5. Dr. Beebe continues to represent NCI on the NCHS group advisory to the Director with respect to the National Death Index (NDI). State registrars are increasingly vocal about certain aspects of the operation of the NDI, especially the high proportion of false positive matches resulting from the present NDI matching criteria. Increasingly the states are duplicating NDI procedures governing access to death certificate information. Work is proceeding under the contract to explore the cost and feasibility of "retro-fitting" the NDI for some period prior to its present initial year, 1979. Adequate funding for a fully operational "retrofit" is not yet in sight, however.

6. Exploitation of the VA hospital discharge file continues to increase. The Medical Follow-up Agency of the National Research Council is bringing in for medical review by NCI investigators the VA hospital records needed for their specific research projects. Additional rosters have been created from the file at the request of investigators in the Program and the record review is proceeding satisfactorily. The VA files for discharges for the years 1986-87 have been received and integrated into the main file, and a more satisfactory method of calculating hospital discharge rates has been developed and used to create systematic cause-specific rates for reference by users of the file. The size of the file is such that considerable programmer time is required to make it manageable for the purposes of the Program.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05280-06 CEB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Carcinogenic Effects of Ionizing Radiation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	G. W. Beebe	Statistician (Health)	CEB	NCI	
Others:	C. E. Land	Statistician	REB	EBP	NCI
	J. D. Boice	Chief	REB	EBP	NCI
	B. W. Wachholz	Chief	REB	CPCP	NCI

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	1.3	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A-bomb survivors, Atomic Energy Commission - Department of Energy workers, the population exposed to fallout from atmospheric tests at the Nevada Test Site, etc., have been studied for their potential to provide low-dose risk estimates for radiogenic cancer. Only some combination of experimental and theoretical work, with epidemiologic studies at higher doses, will provide a reliable guide to such risks. Sources of variation in risk estimates for radiogenic cancer are explored for their significance to research on carcinogenic mechanisms and to give direction to epidemiologic research. Dr. Beebe serves as Assistant Project Officer for the study of thyroid nodules in the high background area of China. He also represents the Department of Health and Human Services on the Science Panel of the Committee on Interagency Radiation Research and Policy Coordination, and NIH on the Public Health Service Group for Input and Communication Regarding Radiation Protection Activities.

Project Description

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

G. W. Beebe	Statistician (Health)		CEB	NCI
C. E. Land	Statistician	REB	EBP	NCI
J. D. Boice	Chief	REB	EBP	NCI
B. W. Wachholz	Chief	REB	CPCP	NCI

Objectives:

1. To evaluate the carcinogenic risk of low levels of ionizing radiation.

2. To determine the limits of knowledge of the carcinogenic effects of ionizing radiation and suggest research needed to extend that knowledge.

3. To suggest how knowledge of differential risks of cancer from exposure to ionizing radiation may be used in research on carcinogenic mechanisms.

Methods Employed:

A continuing analysis is made of the literature on the carcinogenic effects of ionizing radiation. Critical reviews are prepared and needed research outlined. Membership on various research committees provides opportunities for both gaining new information and testing the soundness of interpretations.

Major Findings:

1. A variety of exposures to ionizing radiation were studied for their potential contribution to the estimation of the carcinogenic effects of low doses. From none of them did it seem likely that low-dose estimates of any considerable scientific or practical value would be forthcoming.

2. Dr. Beebe is a member of the National Council on Radiation Protection and Measurements Task Force comparing radiation and chemical carcinogenesis and is responsible for a chapter on the human data on radiation carcinogenesis. The Task Force report is in press. As a member of the Science Panel of the Committee on Interagency Radiation Research and Policy Coordination, he has been particularly active in relation to the preparation of the BEIR V report by the National Research Council, to the use of the NIH Radiological Tables by the Veterans Administration, and to the possible need for pre-disaster planning for scientific study of radiation victims. Dr. Beebe chaired the workshop on Epidemiology and Radiation Protection organized by the Organization for Economic Cooperation and Development (OECD) held in Paris in October 1987. His paper, a Critical Review of Current Epidemiological Studies on Members of the Public, is in press at the OECD. He provided advice to the National Cancer Institute of Canada on the program of radiation epidemiology studies it sponsors at the University of

Toronto, and he also serves on the advisory committee for the NRC study of military personnel exposed in the Crossroads tests in the Pacific.

3. Dr. Beebe is the Assistant Project Officer for the study in the NCI Radiation Epidemiology Branch of thyroid nodules in China. Preliminary analyses suggest that nodules in the 2,000 women examined in 1986 are no more frequent in those living in the high background area than in those living in the low background area.

4. Through the efforts of Dr. John Boice of the NCI Radiation Epiedemiology Branch and Dr. Beebe, the Nuclear Regulatory Commission has been persuaded to establish a registry of workers at nuclear power plants. This would permit mortality from cancer to be monitored in relation to occupational dose.

Publications:

Beebe GW. Carcinogenic effects of nuclear radiation. J Wash Acad Sci 1988;78:101-16.

Beebe GW. Critical review of current epidemiological studies on members of the public. In: Proceedings of the workshop on epidemiology and radiation protection. Paris: Nuclear Energy Agency, Organization for Economic Cooperation and Development. (In Press)

Beebe GW. Dose-effect relationships. In: Proceedings of the international symposium on biological effects of low level radiation. Nanjing, China: Society of Radiological Medicine and Protection, Chinese Medical Association. 1987;166-86.

Beebe GW. Studies of cancer among Japanese A-bomb survivors. Cancer Invest. (In Press)

Miller RW. Fetal radiation syndrome. In: Buyse ML, ed. Birth defects encyclopedia. Dover: Alan R Liss. (In Press)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05329-05 CEB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 charecters or less. Title must fit on one line between the borders.)*

Hepatitis B Virus and Liver Cancer in Army Veterans of WWII

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Gilbert W. Beebe Statistician (Health) CEB NCI

COOPERATING UNITS *(if any)*

Medical Follow-up Agency, National Research Council, NAS (J. Norman); Veterans Administration, Six Hospitals (L. Seeff); Liver Diseases Section, DIR, NIDDK (J. Hoofnagle)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	1.3	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standerd unreduced type. Do not exceed the space provided.)*

The study is based on the epidemic of 50,000 cases of viral hepatitis in the United States Army in 1942, traced to yellow fever vaccine prepared by the Rockefeller Foundation and contaminated with a virus of hepatitis, now hown to have been the hepatitis B virus (HBV). A serologic survey to identify the virus with certainty has been completed on 597 men--about 200 who suffered from acute hepatitis during the 1942 epidemic (Group I), 200 who received vaccine from one of the seven contaminated lots but were not clinically ill (Group II), and 200 who did not receive the Rockefeller vaccine (Group III). Two epidemiologic studies are being performed: 1) a mortality study of 55,000 men divided into three cohorts of approximately equal size, each defined as in the serologic survey, with primary liver cancer the chief end-point; and 2) a case-control study of WWII Army Veterans discharged from Veterans Administration hospitals for liver cancer and matched controls, the comparison to be based primarily on immunization history with attention to the lot number of the yellow fever vaccine.

In the serologic survey, testing for anti-HBs and anti-HBc identified the B virus as the source of the infection. In addition, anti-HB levels were high, and only one carrier (HBsAg+) was identified in Group I, none in Group II or III. The mortality study reveals no excess mortality from cirrhosis among either of the two groups infected with the B-virus, and at most a small excess of liver cancer, nothing like that expected from the Asian studies of carriers. The case-control study is still in the process but should be finished during the coming year. A report on the serologic

Project Description

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

G. W. Beebe Statistician (Health) CEB NCI

Objectives:

To confirm epidemiologic opinion that the virus responsible for the 1942 epidemic was hepatitis B virus (HBV); to test the HBV-primary hepatocellular carcinoma (PHC) hypothesis in an area of low natural incidence with a point-source infection of healthy young males; to determine the long-term (40 years) persistence of the type B antigen and antibodies; to contrast, as to later PHC, men with acute icteric hepatitis following yellow fever vaccination with men vaccinated with the same contaminated lots but showing no evidence of clinical disease; to estimate the likelihood of chronic hepatitis in 40-year survivors of infection with HBV; to test the hypothesis that the pathogenesis of HBV-associated PHC requires a prior cirrhotic stage; to explore other aspects of the natural history of viral hepatitis, e.g., its relation to cirrhosis; and to explore host and environmental factors for their possible influence on the association between HBV and PHC.

Methods Employed:

Assays for hepatitis viruses have become available that will positively identify persons with previous hepatitis A or B virus infection and those chronically infected with HBV. Blood has been obtained from about 200 men in each of the three groups described above and tested for serum aminotransferases, HBsAg, anti-HBs, anti-HBc, anti-HAV, HBeAg, HBsAg subtype, DNA-polymerase activity, HBsAg titer, and serum levels of HBV-DNA.

The three cohorts for the mortality study (and the serologic survey) have been defined on the basis of existing records of the Medical Follow-up Agency and the National Personnel Records Center in St. Louis. Establishment of the cohorts was straightforward except for Group II, men who received contaminated vaccine without becoming clinically ill. Because the 1973 fire caused extensive damage to the Army WWII records stored in St. Louis, most immunization records are no longer available and, for most men, vaccine lot number was inferred from their presence in units known (from the records of clinical cases) to have received contaminated vaccine at particular times.

The cohorts have been traced forward for mortality through the records of the VA system and a sample cleared against the National Death Index to check on VA records. Until October 1981 the VA extended a cash burial benefit as well as a flag and a burial plot to all honorably discharged war veterans, and this mortality ascertainment system has been shown to be 95% complete. Death certificate diagnoses of liver cancer and other liver diseases have been investigated through hospital records and available pathology material to refine the comparisons as to risk of death from primary hepatocellular carcinoma. Comparison of the three cohorts has been performed both directly in age-adjusted fashion and by means of standard mortality ratio calculations.

Because the definition of Group II is somewhat indirect, a case-control study is being performed on the basis of VA hospital discharges for primary liver cancer. The case-control study will yield more certain evidence of vaccine lot number than the cohort study, and it is hoped that there will be many more evidential immunization registers in the case-control study than deaths from primary liver cancer in the cohort study. The case-control study alone would be inadequate, however, because the selection of men for VA hospitalization is completely unknown with respect to the variables under study.

VA hospital cases of liver cancer in WWII Army veterans and matched controls are being traced through military records files in St. Louis for evidence of yellow fever vaccine lot number so that a comparison may be made as to the frequency of contaminated lots in each group. The comparison will be restricted to cases (and their controls) of primary liver cancer only.

The serum for the Rockefeller vaccine was obtained from bleedings at Johns Hopkins in 1941-1942. The Johns Hopkins donor book has been obtained together with all correspondence and questionnaires that figured in the epidemiological investigation by the Army and the Rockefeller Foundation in 1942-43. Since blood was drawn from students and staff, and serum lots are tied to the vaccine lots, it may be possible even now to bleed some donors who contributed to the serum pools used to create the contaminated lots. There are some ethical considerations under study, but an effort was made in 1942-43 to inform all donors of the epidemic and its connection with the vaccine.

Because the documentation of the epidemic makes it possible to separate acute cases of clinical hepatitis, and therefore presumably transient infections, from subclinical and potentially chronic infections, the 1942 material provides an opportunity to explore issues that relate to this distinction. The most important one concerns its significance for the carrier state and the likelihood of later liver cancer. Although the present survey does indicate that any excess risk of liver cancer from the 1942 infection is, at most, small, there is a unique set of veterans who were compensated by the Veterans Administration for residuals of hepatitis in 1957. This file is being explored for its possible usefulness in determining whether there was any excess risk of liver cancer, whether the excess risk was indexed by a chronic state in 1957, and whether the clinical and subclinical cases differ in this respect.

Major Findings:

The published report on the serologic survey demonstrated that the cause of the epidemic was the hepatitis B virus. Only one carrier was identified among 392 subjects infected in 1942. Ninety-seven percent of Group I, 76% of Group II, and only 13% of Group III were positive for antibodies to hepatitis B virus. The prevelance of hepatitis A antibody was similar in the three groups. No subject had antibody to hepatitis delta virus. It appears that the hepatitis B antibodies may persist for life. It was calculated that about 330,000 men may have been infected in 1942.

The findings of the large cohort mortality study reveal little or no excess mortality from primary hepatocellular carcinoma, and no excess mortality from cirrhosis of the liver. Although the prevalence of hepatitis B antibody was high in Groups I and II, and antibody titers were also high, apparently the 1942 exposure produced comparatively few carriers and thus led to, at most, a small excess of liver cancer. The suggestion is strong that adult infection with the hepatitis B virus may not produce carriers anything like the frequency expected on the basis of the Asian studies.

Publications:

Sjogren MH, Seeff LB, Hoofnagle JH, Bales ZB, Beebe GW, Norman JW. Persistence of IgM anti-HBc more than 40 years after hepatitis B virus infection. J Med Virol. (In Press)

ANNUAL REPORT OF

THE ENVIRONMENTAL EPIDEMIOLOGY BRANCH
EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1987 through September 30, 1988

The objective of the Environmental Epidemiology Branch (EEB) is to generate and test ideas concerning the environmental and host determinants of cancer by a broad range of epidemiologic studies based on knowledge and application of clinical medicine and oncology, statistical methodology, new developments in carcinogenesis, and resources best available at the national level.

There were no significant organizational changes in the structure of the Branch within the past year. However, two major events outside of the usual research activities did occur. The Branch was site visited by the Division of Cancer Etiology (DCE) Board of Scientific Counselors on February 8 and 9, 1988. This visit reviewed the Branch's research programs since the last site visit in 1983 and our plans for future research activities. The second major event was the physical move of the Branch from offices within the Landow Building, Bethesda, MD to the newly acquired Executive Plaza Building, North in Rockville, MD. This was accomplished during May and June of 1988.

Two senior investigators left the Branch within the past year. Dr. Thomas Mason resigned as Chief of the Population Studies Section to accept a position outside of the government at the Fox Chase Cancer Center in Philadelphia, PA. Dr. Robert Spirtas left the Occupational Studies Section to accept a position with the Contraceptive Evaluation Branch of the National Institute of Child Health and Human Development. Mr. Manuel Gomez, an industrial hygienist, joined the Occupational Studies Section as a cancer expert to assist in our continuing efforts to strengthen the exposure assessment portion of occupational studies. A number of young scientists joined the Branch within the past year in a variety of postdoctoral fellowship positions. These included Drs. Goldstein and Amos, who will be applying their training in statistical genetics and genetic epidemiology to our expanding program in genetics and cancer, and Dr. Caussy who will be continuing his research into the viral etiology of human malignancies. In addition to postdoctoral fellowship opportunities, five students participated in training opportunities through the Student Research Training Program, and Mr. Allen Hildesheim continued to work on a doctoral thesis project at Johns Hopkins School of Medicine. The EEB also continues to provide a focus for training of a number of foreign scientists. In the past year, scientists from France, Italy, Costa Rica, Germany, China, Holland, Sweden, Australia, and Brazil have all spent varied periods of time in the Branch, engaging in collaborative analysis of a number of data sets.

RESEARCH PROGRAM

The Branch conducts a broad-based research program with respect to exposures assessed, types of cancers evaluated, and specific methods employed. In order to summarize these activities, we often group individual studies into categories which describe integrated research programs focused in particular areas.

Descriptive Studies: To identify, systematically, the geographic variation and clustering of cancer mortality, the Branch has analyzed U.S. cancer mortality on a county level. In the past, cancer death rates were computed and reported along with maps illustrating the variation. These patterns were also related to demographic and potential exposure information at the county level, through correlational or hypothesis-generating studies, thus providing a series of etiologic leads that might explain the variations observed.

A major effort in this program area has been the development of an updated Atlas of U.S. Cancer Mortality Among Non-Whites, with a focus on time trends in cancer mortality among non-whites over the 30-year period from 1950-1980. In addition, utilizing data from a population-based tumor registry within a prepaid health plan, an in-depth evaluation of time trends in breast cancer was undertaken. Overall the incidence of this disease has risen 45% from 1960 to the mid-1980s, with the largest increases occurring among women over age 60. Localized and regional diseases have shown similar rates of increase. Availability of receptor assays since the mid-1970s indicates that estrogen receptor-negative cancers rose 25% between the mid-1970s and mid-1980s, while estrogen receptor-positive tumors have gone up an average of 131% during the same time period.

Field Studies in High-Risk Areas: The descriptive studies outlined above are constantly evaluated for observations that might be profitably followed-up with analytical field investigations in high-risk areas of the United States and the rest of the world. Activity in this program area over the past year has focused on studies of pancreatic cancer in southern Louisiana; laryngeal cancer along the Texas Gulf coast; and lung cancer in New Jersey. Internationally, case-control investigations of gestational trophoblastic disease in China, and cancer of the uterine cervix in Latin America were conducted because of the markedly elevated rates of these tumors in these particular areas.

Analysis of the pancreatic cancer study demonstrated twofold excess risks for moderate and heavy cigarette smokers, while alcohol and coffee consumption were unrelated to risk. Analysis of a large number of dietary variables revealed evidence of excess risks associated with pork and rice consumption and a strong protective influence for fruit intake. Analysis of case-control studies of lung cancer in high-risk areas of New Jersey have focused on occupational hazards. Analysis of lifetime occupational histories noted excess risks for masons and tile setters, janitors, printing workers, trucking service employees, and warehousing and storage workers. Occupational determinants were also evaluated for the risk of laryngeal cancer in coastal Texas. Excess risks were noted for work in the transportation, metal manufacturing, construction and maintenance industries, as well as among those exposed to asbestos, paint and diesel/gasoline fumes. Analyses of the case-control study of invasive

cervical cancer in four areas of Latin America have revealed a number of provocative associations. One of the most intriguing, which might help explain the very high rates of this disease in Latin America, is a progressively increasing risk with increase in number of pregnancies, rising to fourfold for a substantial number of women having had 10 or more pregnancies.

Occupational Studies: Epidemiologic studies of occupational groups are valuable, since workers often have heavy and prolonged exposures to suspect carcinogens. Studies of these groups can therefore lead to measures to reduce the risk to workers and can identify the potential hazard of agents which are also found in the general environment. In addition, detailed studies of groups occupationally exposed to known carcinogens can provide insights into the basic mechanisms of human carcinogenesis. The Branch initiates studies in the occupational area to (a) explain unusual geographic distributions of cancer incidence or mortality, (b) identify high-risk subgroups within broad industrial categories, (c) pursue clues provided by animal bioassays or clinical observations, and (d) assist outside agencies or institutions in evaluating the health experience of workers.

A number of investigations are underway to evaluate the risk of several different malignancies associated with the use of agricultural chemicals. A twofold excess risk of leukemia was noted among agricultural extension agents from the U.S. Department of Agriculture who came into contact with pesticides while conducting demonstration projects for farmers. An interview case-control study in Iowa and Minnesota found associations between chronic lymphatic leukemia and non-Hodgkin's lymphoma among farmers using a variety of pesticides 20 or more years before interview.

A case-control study in Connecticut noted an excess of nasopharyngeal cancer, but not sinonasal cancer, among persons holding jobs where contact with formaldehyde may have occurred. Risks rose to over twofold among those with probable exposure to high levels 20 or more years prior to death, consistent with findings for this tumor seen in an earlier cohort investigation conducted by the Branch.

As a follow-up of earlier descriptive analyses which suggested an excess risk of brain tumors among petrochemical workers, a case-control study of individuals dying of this tumor in three locales (Philadelphia, New Jersey, southern Louisiana) was conducted. Some excess risks were related to exposure to solvents and cutting oils. However, the predominant occupational hazard was work in the electrical and electronics industry. Risk of brain tumor rose with duration of employment in the manufacturing or repair of electronic equipment to approximately 12-fold for those who had worked for 20 years or more.

The relationship between bladder cancer and employment in the chemical industry was assessed in the study of approximately 3,000 incident cases and 6,000 population based-controls. Employment in the production of organic chemicals was associated with a 1.3-fold risk among men, and risk increased with duration of employment to 2.4-fold among those employed 20 or more years.

Finally, occupational data from five previous case-control studies in the United States conducted by the Program were analyzed to estimate the proportion of lung cancer in these various geographic areas that could be considered

attributable to well-known occupational carcinogens. These attributable risks ranged from 3% to 17% across these study areas.

Medicinal Agents: The Branch conducts a variety of studies to assess drug-induced cancer. Such studies have been valuable in the discovery of previously unrecognized carcinogenic hazards, and they have allowed insights into mechanisms of carcinogenesis. This has been so, not necessarily because of the presence of a large burden of drug-induced cancer in our society, but rather because the exposure usually involves high doses which can be assessed by standard epidemiologic approaches. In conducting this research, staff members monitor epidemiologic, clinical, and laboratory observations for candidate drugs that can be evaluated for carcinogenic effects utilizing special resources developed by the Branch. This includes the surveillance of clinical trials for long-term effects, follow-up of specific patient populations, intensive case-control investigations, and record-linkage studies within prepaid health plans. In recent years, the focus of this program has been primarily on hormonal medications and cytotoxic drugs, although a variety of other agents have also been evaluated.

Cohort, case-cohort, and case-control investigations have been performed within the context of a cohort of 23,000 users of menopausal estrogens in Uppsala, Sweden. Excess risks of endometrial cancer, with evidence of dose-response relationships with both duration of use and strength of medication, were noted for estrogens unopposed by progestational agents. For those who used only the combination regimen (estrogen plus progestogen), no excess risks were noted. However, those who switched from unopposed to opposed regimens continued to show some excess risk. Evaluations of breast cancer risk revealed a 60% increase in breast cancer after 10 or more years of replacement estrogen therapy. This excess was not diminished by the addition of progesterone to the regimen; in fact the risks were somewhat higher and seen with shorter durations of use of the combination regimen.

A case-control study of childhood leukemia in Shanghai, China, revealed an excess risk associated with the use of chloramphenicol, with some evidence of a duration-response relationship.

The Branch has continued its active program to evaluate the potential carcinogenicity of various cytotoxic agents used in the treatment of cancer and some non-neoplastic conditions. In a cohort investigation of 1,500 patients treated for Hodgkin's disease at one institution, a cumulative risk of malignancy of 17.6% was noted at 15 years of follow-up. The risk of solid tumor development was 13.2% and was largely due to excesses of radiation-related sites in the fields of radiation for Hodgkin's disease. Solid tumor excesses included lung cancer, stomach cancer, soft tissue sarcomas, and malignant melanoma. The cumulative risk of leukemia was 3.3% which plateaued at approximately nine years of follow-up. The risk of non-Hodgkin's lymphoma was 1.6% and has continued to rise with increasing duration of follow-up.

Nutritional Studies: Indirect evidence that diet and nutrition are related to cancer risk is substantial. Recently, the Branch has expanded its activities in this area to test some of the current hypotheses and to generate additional testable hypotheses. Dietary exposures currently being assessed include consumption of specific food groups and food items, such as meat, fruits and vegetables, ethnic dishes, and coffee; macronutrient and micronutrient intake

such as fat, vitamin A, carotenoids, vitamin C, folacin, and trace minerals; general nutritional status; anthropometry; biochemical indices, such as serum cholesterol and serum beta-carotene; and storage and cooking practices. Cancers being studied include those of the colon, rectum, breast, lung, cervix, pancreas, stomach, and larynx.

A follow-up study of over 5,000 women examined in the First National Health and Nutrition Examination Survey (NHANES-I) revealed no relationship between estimates of dietary fat and saturated fat intake at baseline examination and risk of the development of breast cancer over the next ten years. Evaluation of men and women participating in NHANES-I revealed an inverse relationship between overall cancer risk and serum cholesterol measured at baseline. Those in the lowest 20% of serum cholesterol had 1.6 times the risk of malignancy of those in the highest 20%. This excess was apparent for those whose cholesterol was measured more than six years prior to the development of the disease, as well as for those measured just prior to disease. Evaluation of risk by specific anatomical site suggested a pattern of increased risks associated with lower cholesterol for a complex of smoking-related sites.

As noted previously, a variety of field investigations in high-risk areas revealed evidence of diminished risks for a number of malignancies associated with higher levels of intake of fruits and vegetables and various nutrient indices, including carotene and vitamin C. These relationships have been noted in investigations of lung cancer, stomach cancer, laryngeal cancer, pancreatic cancer, and mesothelioma. Most recently, a case-control investigation of in situ cancers of the uterine cervix indicated an elevated risk associated with relatively low dietary intake of vitamin C and particularly with low serum values of beta-carotene. Women with serum beta-carotene values in the lowest quartile had five times the risk of this malignancy as women with values in the top quartile. Large case-control studies of breast cancer and benign breast disease allowed the evaluation of methylxanthine consumption as a risk factor for these tumors. No relationship was detected even at relatively high levels of consumption.

Comprehensive case-control and methodologic evaluations of the role of fecal mutagens and colon cancer are currently underway. Preliminary results indicate that the major fecal mutagen, fecapentaene, is actually excreted in lower amounts in cases than in controls. In addition, an alteration in diet from a very low level of fat intake to a very high level of fat intake does not result in increased excretion of fecapentaene.

Case-Control Studies: The Branch conducts case-control studies of selected cancer sites that are not necessarily limited to high-risk areas or targeted to test one particular hypothesis. These studies may be initiated for tumors with a wide variety of etiologic leads that need to be tested or for tumors for which little is known but which seem right for a "fishing expedition" to generate new etiologic leads.

Studies of breast cancer have focused on several factors in addition to those outlined under medicinal agents and nutrition. In an investigation of 266 cases of breast cancer for whom mammograms done at least four years prior to disease onset were available, a variety of radiologic parenchymal patterns were related to the risk of subsequent breast cancer. Excess risks of two- to threefold were noted for certain parenchymal patterns and these risks varied

by age, family history of breast cancer, and use of menopausal hormones, but were not explained by control for recognized breast cancer risk factors. Of particular note, was that a family history of breast cancer was not a risk factor among women whose parenchymal patterns were considered N_1, the most "normal" of the parenchymal pattern classifications.

A case-control study of 358 patients with ovarian cancer revealed that parity, but not age at first birth, was inversely related to risk. In addition, hysterectomy with preservation of both ovaries was related to a decrease of ovarian cancer risk, while a variety of non-hormonal factors, including smoking and a history of childhood diseases, were not found to be related to risk.

Analyses continued of the National Bladder Cancer Study, involving interviews with 3,000 bladder cancer cases and 6,000 controls. Attention focused on the relationship between fluid intake and bladder cancer risk. There was a significant increase in risk with increasing daily consumption of tap water, but not of other beverages. In addition, the risk associated with increased tap water ingestion was limited to those living in areas served by surface chlorinated community water systems, particularly long-term residents of such areas.

Analyses were also conducted on the National Bladder Cancer Study data to discern the reason for the substantially reduced risk of bladder cancer among blacks compared to whites. The differences could not be explained by differences in risk factor profiles, differences in levels of risk for each risk factor, or by prevalence of exposure to the identified risk factors. Rather, there was some evidence, particularly from stage-specific data, to indicate that the reasons for the deficit may relate to differences in completeness of ascertainment, including differential use of diagnostic services.

An evaluation of the risk of invasive cancers of the uterine cervix in five different locales within the U.S. confirms the presence and independence of multiple sexual partners and age at first intercourse as risk factors for this disease. Parity also emerged as an independent risk factor, similar to that noted in the Latin America study.

Infectious Agents: The discovery of several human retroviruses, notably human T-cell lymphotropic virus, type I (HTLV-I) and human immunodeficiency virus (HIV), and rapid strides in the identification of type-specific papillomaviruses in various tumors, has added new importance to studies of an infectious etiology for some human cancers.

A case-control study of adult T-cell leukemia (ATL) in Jamaica has identified a 35-fold excess risk of ATL for persons seropositive for HTLV-I. A corollary observation is that at least 20% of the cases were negative for this antibody.

Several investigations have focused on the epidemiology of HTLV-I, especially in the West Indies. In the study of sera from 13,500 healthy Jamaican food service employees, the prevalence of antibodies to HTLV-I was 6.7%. There was a marked rise in prevalence with age, and an excess among females which emerged in the third decade of life. There were no apparent differences in prevalence of antibody according to geographic region of the island. A study in Barbados revealed a relationship between antibodies to HTLV-I and Venereal Disease

Research Laboratories test positivity in the general population. A study of homosexuals in Trinidad indicated an excess prevalence of both HTLV-I and HIV. Taken together, these findings indicate that HTLV-I may also be transmitted sexually, albeit less efficiently than HIV. Studies of parenteral drug abusers in New York City, New Jersey, and New Orleans, initiated to study HIV infection, have revealed surprisingly high levels of antibodies to HTLV-I/II. The prevalence is higher in blacks (46%) than whites (11%) and is currently being pursued with more analytic investigations. A serologic survey of the prevalence of HTLV-I in lymphoreticular malignancies from various geographic locales has documented virus-positive cases from Nigeria, Israel, Taiwan, Colombia, United Arab Emirates, Panama, Singapore, Okinawa, and a number of centers in Japan.

An extensive collaborative study investigated the seroprevalence of antibodies to HTLV-I in migrants from Okinawa to Hawaii and their offspring. The prevalence among Okinawa-born migrants was 20%, identical to that on the island of Okinawa itself. Seroprevalence increased with years of residence in Okinawa prior to migration. The offspring of the migrants had a significant increase in seropositivity with increasing age in the absence of an obvious environmental source for exposure, suggesting that virus infections can exist in a latent phase, possibly from birth, with the subsequent apparent seroconversion reflecting an actual reactivation of latent virus infection. In following-up on these observations, it appears that antibody levels among the second generation to be born in Hawaii are substantially lower than their parents. An additional study of U.S. servicemen who had been stationed in Japan and Okinawa, revealed a 3.8% prevalence of seropositivity for HTLV-I, and this prevalence was correlated with the duration of residence in Okinawa.

A series of studies of HIV infection and the acquired immunodeficiency syndrome (AIDS) have also continued. Analyses of cofactors that might affect the development of AIDS among high-risk populations were conducted in several homosexual cohorts, as well as in a cohort of hemophiliacs. The major risk factors for the development of AIDS in these cohorts were a low T-cell count and a rapidly declining T-cell count. Extensive evaluation of HIV infection in parenteral drug users in New Jersey indicated a geographic distribution of seropositivity indicative of spread from the New York City area. In addition, more frequent parenteral drug use in a preceding year was significantly associated with a higher rate of HIV positivity; blacks were more likely than whites to be HIV seropositive; persons enrolled in treatment programs for longer periods of time were less likely to be seropositive; and female drug abusers were as likely as males to be sero-positive. In a one-year follow-up of the subjects in this cohort, the sero-conversion rate was estimated at 4.1%.

A small cohort of female sexual partners of adult hemophiliacs has been followed for three years. No seroconversions were noted among these women in the first two years, but several have converted in the third year. There was a strong positive association between extremely low T-helper cell counts in the hemophiliac and the seroconversion of his sexual partner.

Suggestions that neoplasia of the uterine cervix may be largely due to type-specific papillomavirus infection are being pursued in a variety of studies. In a study of over 700 cases and 1500 controls from Panama the relationship between papillomavirus types 16 and 18 and the risk of this disease was investigated utilizing in situ hybridization techniques on pap smear material.

The relative risk associated with this infection was approximately fivefold, with the risk increasing with increased strength of the positive laboratory assay.

Family Studies: Studies of cancer-prone families provide special opportunities to clarify the role of genetic susceptibility and environmental interactions in carcinogenesis. These investigations are conducted jointly with the Clinical Epidemiology Branch and with clinical and laboratory scientists at NIH and elsewhere. The development of an integrated manual and computerized record-keeping system has provided a framework for an expanding data base that now includes over 2,900 families. Both classical and innovative analytic techniques are being applied to studies of familial aggregations of melanoma, sarcomas, genitourinary tract cancer, multiple endocrine neoplasia type 1 (MEM-1) and the nevoid basal cell carcinoma syndrome.

Studies of familial melanoma and the dysplastic nevus syndrome (DNS) continued to have a high priority. Most of the emphasis this year has been on the utilization of restriction fragment length polymorphisms to map chromosome 1p in an attempt to identify the gene responsible for this particular syndrome. Sixteen new markers have thus far been identified and prospects for identification of the gene in the near future are good. A cytogenetic study of families with hereditary melanoma and DNS revealed an increased number of chromosomal breaks at a variety of positions among those who have this syndrome, compared to unaffected family members. Studies are currently underway to determine whether these breaks are located at so-called fragile sites. A large study of MEN-1 has confirmed the location of the gene on 11q.

Methdologic Studies: Both by design and by the necessities of the types of studies conducted, a variety of methodologic investigations are performed by the Branch. These range from the development and testing of large data collection systems for their applicability to epidemiologic needs, through tests of alternate methods of conducting field investigations, to the adaptation and development of statistical methods for epidemiologic studies.

Potential epidemiologic resources at the National Center for Health Statistics, the Social Security Administration, the Health Care Financing Administration, and the Veterans Administration have all been evaluated and have undergone extensive testing for utility as epidemiologic resources.

It is important to note that all components of the Epidemiology and Biostatistics Program contribute to methodologic research, with particular emphasis in the Biostatistics Branch. In addition, the EEB has embarked on a series of methodologic studies designed to make the rapidly emerging area of biochemical epidemiology, or interdisciplinary studies, more epidemiologically sound than it has been in the past. Included in these activities are evaluations of specificity, sensitivity, and predictive value of a variety of newly-emergent laboratory assays. Replicability of these assays, and a determination of the field conditions and storage practices that may influence results, are also receiving attention. Determinants of the values for a variety of these assays are also being investigated in order to identify potential confounding factors, as well as potential sources of bias in their use. While the entire range of activities in biochemical epidemiology is in need of this basic methodologic work, the Branch is currently emphasizing

efforts in the areas of genetic markers, biochemical markers of nutritional exposures, and laboratory assessments of immune status.

Investigations within this past year have included evaluations in the area of papillomaviruses, fecal mutagens, and T-cell subsets. Cervical-vaginal lavage has been identified as the most effective technique for retrieving DNA for assays for presence of papillomaviruses. In an investigation of the reliability of Southern blot analyses between independent laboratories, 40 identical samples of DNA were evaluated blindly by Southern blot tests in four laboratories with major reputations in this field. The pair-wise comparisons for presence or absence of papillomaviruses ranged between 66% and 97%, while the specification of type among those considered positive agreed between 77% and 96% of the time. Thus, much of the variability between populations which has been reported could conceivably be due to inter-laboratory variability in the assay. Studies of fecapentaene excretion indicated that various elements of the diagnostic workup for a bowel complaint did not systematically change the fecapatene value. In addition, Ames assays of mid-polarity extracts via TA100 salmonella strains reflected almost exclusively the presence of high levels of fecapentaene. Finally, demographic variables including age, race, and sex appear to affect the "normal" values for various T-cell subsets. Particularly provocative was the observation that cigarette smoking (both present and former) was related to significantly reduced levels of natural-killer (NK) cells.

Reviews: A major role of the Branch is to provide comprehensive and critical reviews of etiologic factors in cancer. These reviews take the form of chapters in books, review articles for journals, or, occasionally, reports for various legislative or regulatory bodies. Over 20 such reviews have been published in the past year, covering virtually all of the program areas of research covered by the Branch. Reviews of individual cancer sites have included malignant melanoma, soft-tissue sarcoma, chronic lymphatic leukemia, chemoreceptor neoplasia, and testicular cancer. Reviews of issues in occupational cancer have included the relationship between chromium compounds and respiratory cancer, cancer and pesticide exposures in farmers, and control for cigarette smoking in assessing occupational hazards. Reviews of virus-related malignancies have included AIDS, retroviruses in general, and Epstein-Barr virus-related cancers. Several reviews were conducted of treatment-associated second primary cancers, and specialized topics for review included breast cancer in relation to mammographic parenchymal patterns, diet and fecal genotoxicity, agricultural chemicals in drinking water, and the dysplastic nevus syndrome. Finally, reviews of cancer epidemiology in general were developed for three separate textbooks on cancer.

OTHER ACTIVITIES:

The Branch continued to provide a liaison for epidemiologic research in the National Cancer Program and for environmental cancer studies being conducted in various agencies in the Federal Government. A great deal of advice and support was given to clinicians, experimentalists, public health officials, and many other groups. Staff members served on the editorial boards of various journals, and on advisory groups and committees connected with cancer centers, several Federal and state agencies, and other national and international activities. Staff members also helped in preparing reports on chemical carcinogens and other activities coordinated by the International

Agency for Research on Cancer and the International Union Against Cancer. Several meetings and projects this year were related to bi-national agreements with the People's Republic of China, Italy, France and Japan.

The Branch continued efforts to identify and utilize epidemiologic resources best available at the national level. Initiatives were taken to stimulate and develop cooperative projects with several government agencies possessing routinely collected data resources that can be utilized for epidemiologic studies (e.g., Social Security Administration, Internal Revenue Service, Department of Labor, Bureau of the Census, Veterans Administration and the National Center for Health Statistics). Another important activity of the Branch has been the on-the-job training of staff at the postdoctoral level, the supervision of medical students during their elective periods at school, field research opportunities for doctoral candidates at Schools of Public Health, and the assignment of visiting scientists with variable experience in epidemiology.

Although the Branch encourages an atmosphere of academic freedom and the development of new ideas and approaches, innovations undergo critical review and evaluation through several mechanisms. These include frequent section and branch meetings; close contacts with support service and collaborating groups; various formal review mechanisms by internal and external committees; several working groups (e.g., data resources, female tumors, family studies, and drug studies); interagency committees; the Clinical Center Review Committee involving clinical investigations; careful scrutiny of questionnaires and protocols prior to and during clearance through governmental channels; ad hoc external review groups for major studies (e.g., the acrylonitrile and methylene chloride studies); the NIH Coordinating Epidemiology Committee; and a variety of advisory bodies that oversee Institute activities, notably the Board of Scientific Counselors in the Division of Cancer Etiology.

SUMMARY REPORT

ENVIRONMENTAL STUDIES SECTION

PROGRESS ON RESEARCH CONTRACTS

The studies of the Environmental Studies Section that are supported by the contract mechanism (14--contracts $10,639,404) were initiated to clarify the role of various environmental and host determinants in the etiology of malignant neoplasms. Specifically examined are associations of cancer and nutritional factors, drugs, other life-style factors, and prior disease. The areas covered by these contracts include 1) studies examining breast cancer in Asian-Americans, 2) studies on environmental cancer using prepaid health plans, 3) studies of cancers that occur excessively among blacks, 4) investigations of cervical cancer in Latin America, 5) investigations of rare reproductive tumors, and 6) studies of cancer and drinking water contaminants.

Studies of Breast Cancer in Asian-Americans (3 contracts):

A case-control interview study of breast cancer among women of Chinese, Japanese, and Filipino heritage is being conducted in the San Francisco-Oakland SMSA (Standard Metropolitan Statistical Area), the Los Angeles SMSA, and Oahu, Hawaii--the only areas of the United States at the time the study was initiated with large numbers of Asian-American residents and population-based cancer registries. Since native Japanese and Chinese women have breast cancer mortality rates approximately one-fifth those of white American women, and breast cancer rates rise in successive generations among Asian families who migrate to the United States, this Asian-American study population may provide a sufficiently heterogeneous risk of breast cancer to permit detection of the underlying associations. Gradual adoption of a Western diet is believed to be primarily responsible for the increased cancer risk among Asian-Americans, and it has been hypothesized that diet during childhood and adolescence may be more crucial than adult diet. To assess the role of childhood-adolescent, as well as adult diet, the subjects selected are 55 years of age or less, so that both they and their mothers can be interviewed about the subjects' early diet. In addition to interviewing the subjects, blood samples are being collected for hormone, lipid, and micronutrient assays; urine samples are being collected for additional hormone assays.

Cases are all women, 55 years of age or younger, of Chinese, Japanese, or Filipino ancestry, diagnosed with histologically confirmed primary breast cancer between April 1, 1983 and March 31, 1988 in the San Francisco-Oakland SMSA, the Los Angeles SMSA, and Oahu, Hawaii. Approximately 635 cases are anticipated. Population-based controls, in a 2:1 ratio to cases, are being selected by random digit dialing in San Francisco and Los Angeles and by a household enumeration survey in Hawaii. The interview focuses on diet, life-style, residential history, reproductive and medical history, and use of hormones. The collaborators from each of the three centers have participated with the NCI Project Officers in designing the study protocol and drafting the interview questionnaire. Currently, they are overseeing case ascertainment, control selection (Hawaii only), interviewing, and the collection and initial

processing of blood and urine samples. The analyses and interpretation will be a joint effort between the collaborators at the three centers and the NCI investigators.

Studies on Environmental Cancer Using Prepaid Health Plans (3 Contracts):

The main objective of this series of contracts is the establishment of a collaborative research program which provides the E&B Program with resources that can be used to evaluate promptly hypotheses about environmental causes of cancer. This is accomplished by analysis of information in a prepaid health plan utilizing data recorded over many years on large groups of patients having particular cancers or exposures and comparable individuals without the cancer or exposure. Another objective has been to explore the numerous resources for record linkage within these plans in order to exploit unique opportunities for epidemiologic assessment of cancer risks. Because of the nature of pre-paid health plan records, the primary hypotheses that can be tested involve those associated with the use of therapeutic drugs, medical conditions, surgical and radiologic procedures, occupations, locations of residence, and exposures that are highly correlated with any of these variables.

A number of case-control, record-abstraction studies have been supported whose primary objectives have been evaluation of a variety of medicinal agents and cancer risk. Several of these have focused on hormonal drugs, including an assessment of the risk of endometrial cancer among users of combination estrogen-progestogen regimens, and the relationship between progestogen use and ovarian cancer risk. The risk of breast cancer has been assessed in relation to use of the minor tranquilizer diazepam; and a complex evaluation of the interrelationships between histologic subtypes of benign breast disease, hormonal drug use, and a family history of breast cancer is being performed on a group of 2,615 women with benign breast disease, among whom 124 have subsequently developed breast cancer. Also currently underway is a case-control study of childhood brain tumors and in utero and childhood drug exposures, as well as parental occupation; an assessment of the prevalence of human papillomaviruses in Pap smear slides from women who subsequently developed cervical intraepithelial neoplasia, and the assembling of a cohort of DES-exposed mothers, sons and daughters to initiate a follow-up study. Finally, these plans have been used to assess the descriptive epidemiology of the increases over time of the incidence of breast cancer and malignant melanoma and squamous-cell cancers of the skin.

Studies of Tumors that Occur Excessively Among Blacks (3 Contracts):

In the United States, pancreatic, esophageal, prostatic cancers and multiple myeloma occur more frequently among blacks than whites. To date, the reasons for these black/white differences in cancer risk have not been investigated. The present study will be the first to systematically evaluate reasons for the excess risk of these four cancers among blacks using a large-scale population-based case-control study.

The objectives of this study are: 1) to identify race-specific risk factors for four cancer types--pancreatic, esophageal, prostatic cancers, and multiple myeloma; 2) to estimate the extent to which the risk factors may explain the black/white difference in the incidence rates of the four cancers; and 3) to use laboratory data to relate certain biochemical indicators (e.g., hormones

and trace metals) to the risk of specific cancers, to evaluate the role of genetics in the development of multiple myeloma, and to examine differences in baseline micronutrient levels between blacks and whites.

The study design involves identification of cases of pancreatic, esophageal, prostatic cancer, and multiple myeloma among blacks and whites who are newly diagnosed over the time period 1986-1989 in hospitals located in three geographic areas (New Jersey, Atlanta, and Detroit). Controls are being selected from the population of each of these three areas. All subjects are being administered a standardized questionnaire by a trained interviewer to detect information on potential risk factors for the four cancer types. In addition, blood is being drawn on a sample of prostate cancer cases and controls and on all male multiple myeloma cases.

Investigations of Cervical Cancer in Latin America (1 Contract):

Cervical cancer is recognized as a leading cause of female death throughout Latin America. Cancer registries in Bolivia, Brazil, Chile, Colombia, Cuba, Jamaica, Panama, Puerto Rico and the Antilles document the world's highest cervical cancer incidence rates where invasive cervical cancer equals about half of all male cancers combined. In these high-risk areas, approximately one in every thousand women between ages 30-55 develops cervical cancer each year.

Despite the high rates of cervical cancer, little is known regarding the etiology of this disease in Latin America. In other areas where it has been investigated, the major risk factors include early sexual experiences, multiple sexual partners, sexual intercourse outside marriage, previous abortions, and possibly smoking and oral contraceptive use. The findings regarding sexual behavior suggest that cervical cancer may be caused by a virus (or other microorganism) transmitted during sexual intercourse. Much attention has focused on the possible role of papillomaviruses, although these agents have not yet been implicated with certainty.

The role of female sexual behavior in the etiology of cervical cancer, however, appears to be inconsistent with patterns of disease in Latin America, since female chastity before marriage and fidelity within marriage are central to most Latin cultural values. Thus, it has been suggested that the sexual promiscuity of Latin males, including visits to prostitutes, may be a more important etiologic factor for cervical cancer than the behavior of women. This hypothesis, known as the "male factor" in cervical cancer, is supported by geographic clustering of cervical and penile cancers, and by findings that women, married to men whose previous wives had cervical cancer, have significantly elevated rates of cervical cancer themselves. In addition, a study in England, focusing on female subjects who reported having had only one partner, showed that the relative risk increased with the number of sexual partners their husbands reported.

The present study, for which data collection has just been completed, thus proposes to: 1) identify characteristics of Latin American women that are predictive of risk of developing invasive cervical cancer; 2) identify behavioral characteristics of Latin males that may contribute to the high disease rates; and 3) relate certain biochemical measurements, in both males and females, to risk. Included for study have been approximately 750 women with invasive cervical cancer from four Latin American countries (Colombia,

Costa Rica, Mexico, and Panama) and 1,500 matched controls. Personal interviews were conducted with these women, and blood and cervical scraping material obtained. In addition, the study included male subjects, who comprised the husbands of the sexually monogamous women. These male study subjects were interviewed in conjunction with a physical examination that focused on hygiene, circumcision status and evidence of infection. Blood samples and penile scrapings were also obtained.

Etiologic Investigations of Rare Reproductive Tumors (2 Contracts):

Carcinomas of the vulva and vagina are among the rarest of genital tumors. Little is known about them apart from the fact that they occur significantly more frequently than expected among women with primary cancers of the uterine cervix, leading to the suggestion that these three diseases may share common etiologic factors. The major objectives of this study are to identify environmental exposures of women that predict the risk of developing these tumors (specifically whether the risk factors are similar to those for cervical cancer) and to relate serological indicators (e.g., infectious agents and micronutrients) to risk of these cancers.

The study, which is nearing completion, utilizes a case-control design, with cases consisting of vulvar and vaginal cancers diagnosed over a 30-month period (representing 12 months of retrospective and 18 months of prospective ascertainment) in two geographic areas in the United States--Chicago and the suburbs of Cook County, and upper New York State. A comparison group consisting of two matched neighborhood controls are being chosen for each case in both study sites.

An attempt is made to conduct personal home interviews with each case and control subject. Topics of the interview include: demographic characteristics, socioeconomic status, reproductive history, sexual history, menstrual history, general medical history including history of premalignant vulvar lesions, smoking history, use of contraceptives, and dietary history. Pertinent data is also being abstracted from the medical records of cases. In addition, 30 ml of venous blood is being drawn from both cases and controls in order to measure serological levels of micronutrients and infectious agents.

Vaginal and vulvar cancer have been linked to human papillomavirus (HPV) infection, but the association of different HPV types with different tumors has not been adequately studied. In order to address this question, fresh tumor specimens and cervical scrapes obtained during colposcopic workup of cases will be obtained for a subset of the cases. Probes for HPV types 6, 11, 16, 18 and 31 will be done using southern blot DNA hybridization techniques.

A Case-Control Study of Cancer and Drinking Water Contaminants (1 Contract):

Ecologic investigations and case-control studies suggest that long-term consumption of drinking water from chlorinated surface supplies may enhance the risk of cancers of the bladder, colon, rectum, and possibly other sites. These findings may be related to the elevated levels of trihalomethane and other by-products of chlorination found in chlorinated surface water, as compared to chlorinated or nonchlorinated water from subsurface aquifers. In addition to

chlorination by-products, many other water contaminants are found in the U.S. water supplies, especially those located in agricultural areas where pesticide residues and soluble components of fertilizer are present in runoff.

The present investigation is a population-based study in the state of Iowa that uses mail questionnaires to collect information from cases (or surrogates) and controls. The study proposes to determine the risk of incident cancers of the colon, rectum, bladder, kidney, brain, and pancreas that may be associated with source of drinking water. An exposure assessment component of the study entails the collection and analysis of several hundred water samples for trihalomethanes, pesticide residues, and nitrates. Modelling of levels of these compounds in water supplies throughout Iowa will be used to estimate past exposures of respondents. Included in the study will be approximately 3,400 cases and 1,500 controls.

Expansion of an Ongoing Case-Control Study of Cancer and Drinking Water Contaminants (1 Contract):

A two year continuation of the "Case-Control Study of Cancer and Drinking Water Contaminants" will include 800 additional cases of bladder cancer and appropriate controls to add to the 600 bladder cases in the original study. This will permit us to evaluate further risk associated with consumption of chlorinated surface water, and explore the question of interaction with other risk factors, such as cigarette smoking.

ENVIRONMENTAL EPIDEMIOLOGY BRANCH

RESEARCH CONTRACTS ACTIVE DURING FY 88

ENVIRONMENTAL STUDIES SECTION

Institution/Principal Investigator/ Contract Number	Title
Northern California Cancer Program Donald Austin NO1 CP 21010	Studies of Breast Cancer in Asian-Americans
University of Southern California Brian Henderson NO1 CP 21038	Studies of Breast Cancer in Asian-Americans
Cancer Center of Hawaii Abraham Nomura NO1 CP 21036	Studies of Breast Cancer in Asian-Americans
Kaiser Foundation Research Institute Los Angeles, California Harry Ziel NO1 CP 11038	Studies on Environmental Cancer Utilizing Prepaid Health Plans
Kaiser Foundation Research Institute Oakland, California Gary Friedman NO1 CP 11037	Studies on Environmental Cancer Utilizing Prepaid Health Plans
Kaiser Foundation Research Institute Portland, Oregon Andrew Glass NO1 CP 11009	Studies on Environmental Cancer Utilizing Prepaid Health Plans
Michigan Cancer Foundation Marie Swanson NO1 CP 52090	Investigations of Tumors that Occur Excessively Among Blacks
New Jersey State Dept. of Health Annette Stemhagen NO1 CP 51089	Investigations of Tumors that Occur Excessively Among Blacks
Emory University Ray Greenberg NO1 CP 51092	Investigations of Tumors that Occur Excessively Among Blacks
Gorgas Memorial Institute William C. Reeves NO1 CP 41026	Investigations of Cervical Cancer in Latin America

Health Research, Inc. N.Y. State Dept. of Health Philip Nasca NO1 CP 51022	Etiologic Investigations of Rare Reproductive Cancers
Illinois Cancer Council Katherine Mallin NO1 CP 51093	Etiologic Investigations of Rare Reproductive Cancers
University of Iowa Charles Lynch NO1 CP 51026	Case-Control Study of Cancer and Drinking Water Contaminants
University of Iowa Charles Lynch NO1 CP 85614	Expansion of an Ongoing Case-Control Study of Cancer and Drinking Water Contaminants

SUMMARY REPORT

POPULATION STUDIES SECTION

PROGRESS ON RESEARCH CONTRACTS

The Population Studies Section has responsibility for the acquisition and utilization of resources to facilitate epidemiologic studies. These studies range from descriptive to analytic, including case-control and cohort studies. Liaison is maintained with government and nongovernment sources to realize these objectives. That which follows are summaries of several activities within the Section which were supported by research contracts.

Lung Cancer in New Jersey: Case-control studies of incident lung cancer among male residents of previously identified high-rate areas of New Jersey, as well as a statewide study among females, are being analyzed. Among males, emphasis has been given most recently to occupation. Masons and tilesetters, janitors and cleaners, printing workers, and trucking service, warehousing and storage workers had significantly high risk overall and for short duration of employment. Although the excess risk for all shipbuilding workers was primarily among those with reported exposure to asbestos, the risk was also high among welders, burners, sheetmetal workers and boilermakers, with no reported asbestos exposure.

Among females, analyses are pursuing the potential role of hormonal factors as they relate to the risk for lung cancer by cell type. Utilizing reproductive and smoking histories, each woman's smoking practices are quantified at distinct times during her reproductive life: menarche, first pregnancy, subsequent pregnancies, use of replacement estrogens, and menopause (both natural and surgical). Emphasis is given to the potential facilitation of the effect of smoking by hormonal factors (e.g., replacement estrogens) as well as the potential for an independent hormonal effect. Additional analyses are pursuing the roles of smoking characteristics and diet as they relate to the risk of lung cancer by cell type.

This case-control study of incident lung cancer among all females in New Jersey has provided an opportunity to investigate the role of reproductive factors in the etiology of lung cancer. Preliminary analyses suggest that certain subsets of the population who have used replacement estrogens for menopausal symptoms are at increased risk of lung cancer. Nonsmoking women, age 63 or older, who never had an oophorectomy with a history of hormone use are at increased risk for lung cancer (O.R.=4.98, 95% C.I.:1.77-14.02). Hormone use prior to 1960 conveyed the greatest risk (O.R.=6.74, 95% C.I.:1.84-24.66).

Among nonsmokers, hormone use and passive smoking exposure from a spouse were highly correlated. Older, non-oophorectomized women with both of these exposures carried an increased risk of lung cancer (O.R.=4.23, 95% C.I.:1.56-11.49) relative to those women having neither exposure. Women having one exposure, but not the other were not at any increased risk. There was some suggestion of an increased risk of lung cancer among heavy smokers who use estrogens (O.R.=2.4) which was not statistically significant.

Detailed smoking data collected for both males and females in the New Jersey lung cancer study represent a unique resource to examine smoking practices over the entire lifetime of the individual, focusing on changes in intensity over time. These data will allow for comparisons between male and female patterns and for observing changes in patterns over calendar time. Traditional measures of average lifetime smoking measures are being examined in light of these detailed smoking profiles available for each study subject.

Lung Cancer in Louisiana: Analysis of dietary practices among respondents of this case-control study of lung cancer in southern Louisiana showed a strong protective effect of fruit intake, independent of level of vegetable intake. Cigarette smoking appears to be the major risk factor, with persons who rolled their own cigarettes at the highest risk, presumably because of the usually higher tar content of these cigarettes. A significant dose-response was seen for squamous/small cell tumors by tar content of usual brand of cigarettes smoked, but no trend was noted for adenocarcinomas.

Ongoing occupational analyses of data from white males in the Louisiana lung cancer study revealed increased risks among several industrial categories. A consistent pattern of increased lung cancer risks among nonmokers and light smokers with little or no increase among the moderate and heavy smokers was observed for a number of exposure categories, particularly employment in the lumber manufacturing and construction industry.

Mesothelioma in Southern Louisiana: This case-control study of mesothelioma in southern Louisiana identified 37 cases of malignant mesothelioma (32 pleural, 5 peritoneal) during 1979-81. As expected, potential exposure to asbestos was associated with a sixfold risk; cigarette smoking did not appear to be a risk factor. An examination of potential or reported exposures to other dusts revealed a twofold, but insignificant, risk for exposure to wood dust. After controlling for asbestos exposure, there appeared to be a protective effect of vegetable intake, particularly carotenoid-containing vegetables.

Lung Cancer in Gulf Coast Texas: Collaboration with Dr. Buffler's staff at the University of Texas School of Public Health (UTSPH) continued for the analysis of this study of approximately 1000 lung cancer cases and 1000 controls resident in a six-county area of Gulf Coast Texas, including Houston. Preliminary analysis of the data for women showed very high smoking prevalence, with risk patterns for women very similar to those of men who smoked at the same level. Significantly elevated risks associated with smoking were seen for each of the major histologic types, although risks for adenocarcinoma were substantially lower than for squamous cell or small cell tumors. Analysis of occupational factors is ongoing by the Texas staff.

Data are currently being examined to evaluate whether families of lung cancer cases have a higher prevalence of cancer, particularly smoking-related cancers, than do controls. Preliminary analysis indicates that cases were more likely than controls to have reported any cancer in a first-degree relative (O.R.=1.4), although no increasing trend in risk was seen with increasing proportion of family members affected.

Laryngeal Cancer in Selected Texas Counties: Analysis of this case-control study among white male residents in a six-county area of Gulf Coast Texas, including Houston, showed a significantly elevated risk for squamous cell carcinoma of the larynx associated with cigarette smoking (RR=4.7), alcohol consumption (RR=2.1), and with reduced consumption of fruits and vegetables (RR=1.8). Excess risks were also seen for men employed in the transportation, metal fabricating, construction and maintenance industries, and for men potentially exposed to paint and diesel/gasoline fumes. A further examination of dietary factors by a UTSPH master's student showed a significant protective effect of carotenoid-containing vegetables. Examination of the combined risks for cigarette and alcohol consumption showed that these factors act in a manner intermediate between additive and multiplicative.

U.S. uranium miners are an occupational cohort on whom extensive data are available. Sputum samples were collected periodically betwen 1956 and 1980 from uranium miners who were enrolled in a long-term mortality study. This study population is comprised of approximately 3200 white and 800 American Indian miners. Each sputum sample was classified on the basis of the most severely abnormal cells found. Analyses using transitional probability matrices have found that the increasing level of severity of cytology is not influenced by extent of exposure to radiation; the change from mild to moderate atypia is the most likely transition; that the probality of this transition increased significantly with increasing level of smoking; and that once a miner stops smoking, the probability of the regressive transition from moderate to mild atypia doubles to be equal to the probability of this transition among persons who have never smoked.

Biomedical Computing

Development of Statistical Methods: Work continued in the area of statistical methods development. (1) A measure of variation used for exploratory data analysis was modified to eliminate the high correlation of the variability with the level of site-specific cancer mortality rates. This measure enabled us to quantify and compare the variablitity of the distribution of mortality rates across the country by cancer site, leading to the conclusion that the rates for all but one cancer site have become more homogeneous over the past 30 years. (2) For the examination of the interaction of alcohol and smoking on the risk for laryngeal cancer in a case-control study in Texas, a "super-model" was developed that includes, as subsets, most of the models that have been proposed for this type of analysis in the past. This model not only distinguishes between additive and multiplicative risks, but allows for many forms of the relationship between each exposure and disease. (3) For the design of a new case-control study of lung cancer among women in high-risk areas, the sample size determination methods of Whittemore and Smith/Day were extended to consider the effect of adjusting for a categorical confounder via a logistic model. The new methods were implemented using LOTUS, a spreadsheet program now available to show quickly the effects of changing study parameters, such as the expected exposure rate in the population. (4) An asymptotic variance estimator was developed for the Standardized Mortality Odds Ratio for the Occupational Studies Section. This provides a method of testing and confidence limit calculation not previously available. (5) Mathematical methods were developed to predict the nasal cavity volume of dog skulls based on two-dimensional measurements from x-rays; these volumes and other measures

will be correlated with known nasal cancer rates for the various breeds to determine which measurements might best predict cancer risk.

Projects scheduled in the near future include: (1) the application of linear programming techniques to select which foods should be included in a dietary questionnaire in order to accurately predict the category of intake of a particular nutrient with greater than a specified probability; this will be implemented as a simple "expert system," using the food/nutrient data base already in existence; (2) an examination of the accuracy of the variance/covariance estimates of nonlinear model parameters from several quasi-Newton methods which are now available in new statistical packages for the microcomputer.

Development of Computer Programs for Epidemiologic Analysis: Work continued during FY87 on the development of computer programs and macros to facilitate statistical analysis by epidemiologists. A SAS mainframe macro that screens a list of variables for degree of confounding present for each of many exposures was updated to include a new chi-square statistic for heterogeneity of the stratified odds ratios (Tarone's statistic).

Population Estimates: The Bureau of the Census is developing estimates of the resident population of the U.S. at the county level by age, race and sex for the 1980s. We have received estimates through 1984. During FY87 the Bureau will provide annual estimates for 1985. Models have been developed which utilize special censuses, decennial censuses, and medicare registration to provide these estimates. Prior estimates for the 1970s have been revised using the 1980 census. Special emphasis has been given to the development of estimates for the black population at the county level. The Bureau of the Census continues to respond to requests for special population estimates.

ENVIRONMENTAL EPIDEMIOLOGY BRANCH

CONTRACTS ACTIVE DURING FY88

POPULATION STUDIES SECTION

Institution/Principal Investigator Contract Number	Title
Bureau of the Census Sam Davis Y01 CP 20517	Population Estimates by Age, Race, and Sex for 1980's
Capital Systems Group, Inc. Paul Proteau N01 CP 61003	Biomedical Computing - Design and Implementation (For the Environmental Epidemiology Branch)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04378-13 EEB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

U.S. Cancer Mortality Survey and Related Analytic Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

PI:	L. Pickle	Health Statistician	EEB	NCI
Others:	N. Dalager	Epidemiologist	EEB	NCI
	R. Falk	Health Statistician	EEB	NCI
	B. Stephenson	Computer Specialist	BB, DCE	NCI
	R. Ramsbottom	Computer Specialist	BB, DCE	NCI
	M. Stump	Chief, Info. Resources Section	BB, DCE	NCI

COOPERATING UNITS *(if any)*

National Center for Health Statistics, Bureau of the Census (Sam Davis); Environmental Protection Agency (Wilson Riggan)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Population Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.25	3.0	0.25

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The overall objective of this project is to examine the cancer mortality experience in the United States relative to cancer etiology. Special emphasis is placed upon the selection of areas in the U.S. for intensive study. Publications from this area of interest have facilitated the design of ongoing analytical investigations to test specific etiologic hypotheses.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

L. Pickle	Health Statistician	EEB	NCI
N. Dalager	Epidemiologist	EEB	NCI
R. Falk	Health Statistician	EEB	NCI
B. Stephenson	Computer Specialist	BB, DCE	NCI
R. Ramsbottom	Computer Specialist	BB, DCE	NCI
M. Stump	Chief, Info. Resources Section	BB, DCE	NCI

Objectives:

To examine the cancer mortality experience in the United States relative to cancer etiology. Special emphasis is placed upon the selection of areas in the U.S. for intensive study.

Methods Employed:

Methods for the descriptive component of this project involve computer analysis of more than nine million death certificates by site, sex, race, county, and age. The investigation is ongoing, updated each year, and expanding. Data for all causes of death are utilized from 1968. For the analytic phase of this project the usual approach is that of a case-control study of incident site-specific cancers among residents of the selected geographic areas utilizing general population comparison persons.

Major Findings:

The major activity on this project this fiscal year has been an attempt to identify places (State Economic Areas) within the U.S. which are experiencing differential rates of change of site-specific cancer mortality among nonwhites relative to the country as a whole. Ongoing analyses of this data resource suggest that nonwhite prostate cancer mortality is increasing rapidly in the Southeastern U.S.

Long-standing excesses of lung and other tobacco-related malignancies have been noted for some time in southern Louisiana. In addition, while the cancer maps showed little evidence of clustering of high rates for pancreas cancer, southern Louisiana was one of the few areas of such clustering. Finally, while stomach cancer rates were elevated among Blacks, little evidence of clustering was seen in the maps for nonwhites, with the notable exception of a broad area of elevated rates in southern Louisiana. For all these reasons, a series of hospital-based, case-control studies of lung (n=1338), pancreas (n=363) and stomach (n=391) cancers was initiated in this area in collaboration with Louisiana State University.

For lung cancer, particularly excessive risks were noted for the use of hand-rolled cigarettes, a practice common among the Cajun population of the region.

Analysis of the pancreatic cancer study demonstrated twofold risks for moderate and heavy smokers, while alcohol and coffee consumption were unrelated to risk. Analysis of a large number of dietary variables yielded evidence of excess risks associated with pork and rice consumption and a strong protective influence for fruit intake.

The Gulf coast areas of Texas were noteworthy for marked excesses of respiratory cancers (primarily lung and larynx). These observations, along with correlational studies suggesting a hazard associated with the presence of the petrochemical industry led to investigations of these two sites in collaboration with the University of Texas.

A population-based study of 935 lung cancer cases and 948 controls revealed excess risks among men associated with employment in gas/oil extraction, construction, chemical, metals and transportation industries. The anticipated associations with cigarette smoking were seen for both sexes. However, the smoking prevalences among women were the highest we have yet encountered in our field studies, suggesting that this may be responsible for the excess rate among females in this area.

Analysis of the occupational histories for the 209 laryngeal cancer cases and 250 controls uncovered excess risks in the transportation, metal fabricating, construction and maintenance industries, as well as among those exposed to asbestos, paint and diesel/gasoline fumes.

Perhaps the most prominent state highlighted by the cancer maps in the mid 1970s was New Jersey, which was promptly labeled "cancer alley" by the lay press. Over the years the EEB has pursued a number of these excesses in collaboration with the New Jersey State Department of Health. Most recently, a series of population-based studies of lung cancer (763 White males, 296 Black males, and 994 females) have come to analysis. While most of the analyses still have to be done, a few findings have emerged. Analysis of lifetime occupational histories noted excess risks for masons and tilesetters, janitors, printing workers, trucking service, warehousing and storage workers. Analyses have also been done exploring the relationship between tar content of cigarettes smoked and risk of lung cancer and clarifying the protective role of fruit, vegetables and carotene consumption.

Publications:

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Correa P, Fonthem E, Chen V, Craig J, Falk R, Pickle LW. Diet, nutrition, and cancer. J La State Med Soc 1988;140:43-53.

Falk RT, Pickle LW, Fontham ET, Correa P, Fraumeni JF, Jr. Lifestyle risk factors for pancreatic cancer in Louisiana. A case-control study. Am J Epidemiol (In Press)

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Pickle LW, Mason TJ. Mapping cancer mortality in the United States. In: Thornton, I, ed. Proceedings of the first international symposium on geochemistry and health. Middlesex: Science Reviews Ltd., 1987;72-83.

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Pickle LW, Mason TJ, Howard N, Hoover R, Fraumeni JF Jr. Atlas of U.S. Cancer Mortality Among Whites, 1950-1980. DHHS Publ. No. (NIH) 87-2900.

Pickle LW, McCormick GP. Estimation of the variance matrix for maximum likelihood parameters by quasi-Newton methods. In: Wegman, E, ed. Proceedings of the 20th annual symposium on the interface: computing science and statistics. Alexandria: ASA (In Press)

Schiffman MH, Pickle LW, Fontham E, Zahm SH, Falk R, Mele J, Correa P, Fraumeni, JF Jr. A case-control study of diet and mesothelioma. Cancer Res (In Press)

Schoenberg JB, Stemhagen A, Mason TJ, Patterson J, Bill J and Altman R. Occupation and lung cancer risk among New Jersey white males. JNCI 1987;79:13-21.

Wilcox HB, Schoenberg JB, Mason TJ, Bill JS, Stemhagen A. Smoking and lung cancer: risk as a function of cigarette tar content. Prev Med (In Press)

Winn DM, Pickle LW. Smokeless tobacco and cancer in women: implications for epidemiologic research. Women Health 1987;11:223-4.

Ziegler RG, Wilcox HB, Mason TJ, Bill JS and Virgo PW. Seasonal variation in intake of carotenoids, vegetables, and fruits among white men in New Jersey. Am J Clin Nutr 1987;45:107-14.

CONTRACTS IN SUPPORT OF THIS PROJECT

BUREAU OF THE CENSUS (Y-CP2-0517)

Title: Population estimates by Age, Race, and Sex for the 1980's

Current Annual Level: $7,500.00

Person Years: 1.0

Objectives: To provide estimates of the U.S. population at the county level which are consistent with the NCI's place codes which were utilized in earlier publications.

Major Contributions: This support contract is essential for the continuation of this project, for it provides estimates of populations at risk for cancer at the county level.

CAPITAL SYSTEMS GROUP, INC. (N01-CP6-1003)

Title: Biomedical Computing - Design and Implementation

Current Annual Level: $1,463,013.00

Person Years: 28.0

Objectives: This contract provides computer support for intramural research activities of the Environmental Epidemiology Branch.

Major Contributions: The contractor provided systems design and analysis support for this project. Efficient file design and modification of computer graphics systems were the major contributions to this project.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04410-12 EEB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of Persons at High Risk of Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M.A. Tucker	Chief, Family Epidemiology Section	EEB	NCI
Others:	W.A. Blattner	Chief, Viral Epidemiology Section	EEB	NCI
	D.L. Mann	Chief, Biochemical Epidemiology Sec.	LHC	NCI
	S.J. Bale	Senior Staff Fellow	EEB	NCI
	N.E. Caporaso	Medical Staff Fellow	EEB	NCI
	G.L. Shaw	Medical Staff Fellow	EEB	NCI
	Y. Liu	Fogarty Fellow	EEB	NCI
	R.C. Young	Chief	MB	NCI

COOPERATING UNITS *(if any)*

Biological Research Faculty & Facility (T. Shimada); Braton Biotech (S. VedBrat); Biotech Laboratories (A. Bodner); Westat, Inc. (J. Cahill); CSG/ORI (K. Boyd/D. Switalski)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Family Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7.5	6.2	1.3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to (a) conduct and coordinate interdisciplinary studies on members of cancer-prone families and other high-risk populations to clarify the role of genetic mechanisms and host-environmental interactions in human carcinogenesis; and (b) assess, quantify, and elucidate the determinants of the cancer risks associated with therapeutic exposure to cytotoxic drugs. Project staff also conduct or collaborate with other EEB investigators in epidemiologic case-control studies of specific cancers or cohort studies of specific exposures that are particularly relevant to this project. A series of project resources has been developed in support of our research, including (1) a computerized registry of cancer-prone families; (2) a biospecimen repository which processes, stores and distributes biological samples from persons at high risk of cancer; (3) a fibroblast repository/tissue culture facility; and (4) a series of contract-supported laboratories which provide immunologic, cytogenetic, and DNA repair assay capabilities. Persons at high risk of cancer are evaluated clinically and donate biological samples. Clinical, epidemiologic, genetic, and laboratory studies are combined to elucidate mechanisms of cancer susceptibility. The familial melanoma project is a prototype of this approach, in which clinical (dysplastic nevi), genetic (autosomal dominant transmission of a gene possibly linked to the Rh locus) and biological (enhanced sensitivity to the cytotoxic and mutagenic effects of UV radiation) risk factors have been identified. The therapeutic administration of cytotoxic drugs provides an opportunity to explore the carcinogenic effects of these agents in man. Case-control and cohort studies of cancer patients treated with specific cytotoxic drugs are conducted. These studies have documented differences in leukemogenic potential among specific alkylating agents, and increasing risk of bone cancer associated with alkylating agents independent of radiation therapy has been demonstrated.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

M.A. Tucker	Chief, Family Studies Section	EEB	NCI
W.A. Blattner	Chief, Viral Epidemiology Sec.	EEB	NCI
D.L. Mann	Senior Investigator	LHC	NCI
S.J. Bale	Senior Staff Fellow	EEB	NCI
J.F. Fraumeni, Jr.	Associate Director	E&B	NCI
R.N. Hoover	Chief	EEB	NCI
J.D. Boice, Jr.	Chief	REB	NCI
N.E. Caporaso	Medical Staff Fellow	EEB	NCI
G.L. Shaw	Medical Staff Fellow	EEB	NCI
Y. Liu	Fogarty Fellow	EEB	NCI
M.C. Fraser	Nurse Epidemiologist	EEB	NCI
J.J. Mulvihill	Chief, Clinical Genetics Section	CEB	NCI

Objectives:

To document the occurrence of cancer in high-risk groups and to study such groups by clinical, epidemiologic and laboratory investigations in an effort to elucidate genetic mechanisms and host-environmental interactions contributing to carcinogenesis. To develop educational materials and provide counseling to study participants. To coordinate the distribution of tissue and blood specimens obtained from high-risk persons to interested investigators for etiologic studies by cytogenetic, immunologic, endocrine, biochemical, tissue culture and other methods. To apply innovative analytic approaches to these studies, including statistical genetic methods.

Methods Employed:

Protocols for study of high-risk populations are developed, outlining study aims and methods, and are reviewed by the Section's professionals to maximize efficient use of personnel and laboratory resources. Study subjects are interviewed with respect to medical, occupational, and environmental history, as well as familial occurrences of cancer and other disorders, and are examined for clinical features associated with heightened cancer risk. Family medical history is systematically documented utilizing a family medical history questionnaire. Clinical history is documented using vital records and hospital and physician charts, and operative specimens are submitted for review by collaborating pathologists. Data are abstracted, entered, and verified on a computerized record keeping system. Specialized questionnaires are developed for documenting specific etiologic information. Biologic specimens are collected from informative study subjects, stored in biospecimen repositories, and transmitted to collaborating or contract laboratories. For studies of cytotoxic drugs, standard cohort and case-control methods are used.

PROJECT 1: CLINICAL, BIOLOGICAL AND GENETIC STUDIES OF CANCER-PRONE FAMILIES

Family Studies Resources:

An integrated computerized and manual data base continues to provide support for our registry of cancer-prone families (now numbering more than 2900) which forms the core resource for this project. These families comprise a nonpopulation-based series of kindreds ascertained from NIH and extramural physicians and nurses, and by self-referral of concerned family members. This system includes a computerized clinical information file which can be linked to a biospecimen inventory and laboratory-generated data files, thus simplifying record keeping and permitting computer-based data analysis. An additional component is a computerized patient, test and record tracking system designed to permit efficient monitoring of the information generated. Three contracts, shared with the Viral Epidemiology Section, provide critical laboratory support to these studies: (a) a laboratory for the processing, storage and distribution of biological specimens (Biotech Research Laboratories); (b) a laboratory for the establishment, expansion and storage of fibroblast cell lines (Biological Research Faculty and Facility); and (c) an immunogenetics laboratory for HLA-typing and in vitro immune function testing (Braton Biotech). Contract-based resources, shared with the Clinical Epidemiology Branch, provide laboratory support for genetic linkage studies (Integrated Genetics, Inc. and University of California at Los Angeles). Our cooperative arrangement with the NIH Cancer Nursing Service continues to provide us with the invaluable services of an Epidemiology Research Nurse. Our statistical geneticist continues to provide a critical quantitative approach to the design and analysis of studies conducted in members of cancer-prone families.

Malignant Melanoma

This project is now in its twelfth year, employing the interdisciplinary research strategy outlined above. The major focus of effort in familial melanoma has been the attempt to map the gene.. Linkage analyses have continued, with the development of additional DNA probes to try to localize the gene. Additional areas have been excluded (Gm on 14q). The study to evaluate fragile sites in affected members of melanoma-prone families has continued. The data have been collected and the analysis is in progress.

The pilot study of dysplastic nevi in a dermatology practice has continued. The data has been collected, and analysis has just begun. The design of the projected multicenter cutaneous melanoma case-control will depend on the results of the pilot. In collaboration with investigators from the Danish Cancer Registry, a population-based case-control study from East Denmark was analyzed. Important host risk factors that were identified include the presence of nevi or freckles, and hair color. Intermittent sun exposure and sunburning as a child were the most important sun-related risk factors.

Genitourinary Cancer

Members of previously studied bladder cancer families in the younger generation are now approaching the age when they might start to develop bladder cancer. Members of these families prone to bladder cancer are being recontacted to undergo an extensive clinical and pharmacogenetic evaluation.

Nevoid Basal Cell Carcinoma Syndrome:

Studies to find the genomic location of the NBCC gene are ongoing. Linkage studies using 26 polymorphic biochemical markers are complete and investigations using DNA markers are still in progress.

In collaboration with the Dermatology Branch, we are beginning to analyze the relationship between lifetime sun exposure and development of basal cell carcinomas in affected individuals. An educational "UPDATE" has been developed and is sent bi-annually to all family members who have participated in the study as well as to referring physicians and other interested dermatologists and geneticists.

Multiple Endocrine Neoplasia Type I (Wermer's Syndrome):

One hundred fifteen members of a single, well-characterized kindred, including 44 affected individuals have been evaluated. Analysis of linkage with 26 polymorphic biochemical markers has been completed and presented at an international meeting. Linkage studies using DNA markers are nearly complete on this family and confirm the finding of a gene for MEN1 located on human chromosome 11q. A multipoint linkage analysis of this region is in progress.

DNAs are being prepared from individuals in six other families with MEN1, or variants of the syndrome, in order to determine the extent of genetic heterogeneity in the disorder.

Biochemical Epidemiology of Lung Cancer:

As one of the initial EEB efforts in applying sophisticated laboratory probes to an epidemiologically-designed study, a case-control study of lung cancer is in the field.

To date, 180 study subjects have been accrued. Preliminary analysis of 62 cases, 37 chronic obstructive pulmonary disease (COPD) controls, and 26 other cancer controls confirms that the debrisoquine extensive metabolizer phenotype is related to the risk of lung cancer. Laboratory components of this study include evaluating 1) a RFLP marker thought to be close to the gene for the enzyme for debrisoquine metabolism; 2) polymorphisms at the c-H-*ras* locus variable tandem repeat region; 3) urine mutagenesis; 4) urinary n-nitrosoacids; and 4) 4-aminobiphenyl hemoglobin adducts.

Reanalysis of Idle's data set continues. Redefinition of metabolic phenotypes has improved the estimation of gene frequencies. The analysis of

the occupational data has shown an additive effect of the extensive debrisoquine metabolic phenotype and asbestos or polyaromatic hydrocarbons. A large multicenter case-control study of lung cancer has been initiated to confirm the above observations.

PROJECT 2: THE CARCINOGENICITY OF CYTOTOXIC DRUGS

Employing various strategies, this project is designed in collaboration with the Radiation Epidemiology Branch (REB), NCI, to (1) assess and quantify the cancer risk associated with specific cytotoxic drugs; (2) seek clinically relevant differences in risk among the various agents studied; (3) determine whether cancer risk increases as a function of drug dose; (4) learn whether there is an interaction between cytotoxic drugs and therapeutic radiation in cancer risk; (5) elucidate host characteristics which might permit identifying subgroups of patients which are unusually susceptible to treatment-related cancers; and (6) gain insights into the mechanisms of human carcinogenesis.

Among the strategies employed are: (1) cohort studies of patients with a particular index disease; (2) randomized cohort studies, similar to (1) except that patients are participants in randomized clinical trials; and (3) case-control studies of patients with second cancers.

Hodgkin's Disease:

A cohort study of 1500 patients with Hodgkin's disease treated at Stanford University Medical Center was completed. The cumulative risk of second cancers was 17.6% at 15 years. Most of the second cancers were solid tumors, the most common of which were lung cancer, stomach cancer, and melanoma. There was no difference in the 100-fold increased risk of leukemia between those patients treated with chemotherapy alone, or combined modality therapy.

Childhood Cancer:

Analysis of the data collected in collaboration with the Late Effects Study Group regarding the occurrence of subsequent cancers in survivors of childhood malignancy continues. Analyses of thyroid cancer as a second tumor show a strong dose-response with radiation therapy. There was no significant effect of alkylating agent chemotherapy. Preliminary analyses of connective tissue sarcomas also shows an effect of alkylating agent chemotherapy in addition to radiation therapy.

Publications:

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Chang EH, Pirollo KF, Zou ZQ, Cheung HY, Lawler EL, Garner R, White E, Bernstein WB, Fraumeni JF Jr, Blattner WA. Oncogenes in radioresistant non-cancerous skin fibroblasts from a cancer-prone family. Science 1987;237: 1036-9.

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Spence MA, Sparkes RS, Parry DM, Bale SJ, Cortessis V, Mulvihill JJ. Genetic linkage studies with neurofibromatosis: the question of heterogeneity. J Med Genet 1987;24:527-9.

Spirtas R, Connelly RR, Tucker MA. Survival patterns for malignant mesothelioma: the SEER experience. Int J Cancer (In Press)

Tucker MA. Individuals at high risk of melanoma. In: Elwood M, MacKie RM, eds. Pigment cell. Melanoma and naevi: incidence, interrelationships, and implications. Basel: Karger, 1988;9:95-109.

Tucker MA. Where dysplastic nevi have led us. In: Proceedings of the 18th international symposium of the Princess Takamatsu cancer research fund. Tokyo: Scientific Society Press (In Press)

Tucker MA, Coleman CN, Cox RS, Varghese A, Rosenberg SA. Risk of second malignancies following Hodgkin's disease after 15 years. N Engl J Med 1988;318:76-81.

Tucker MA, D'Angio GJ, Boice JD, Strong LC, Li FP, Stovall M, Stone BJ, Green D, Lombardi F, Newton W, Hoover RN, Fraumeni JF Jr. Bone sarcoma linked to radiotherapy and chemotherapy in children. N Engl J Med 1987;317:588-93.

Tucker MA, Fraumeni JF Jr. Treatment-related cancers following gynecologic malignancy. Cancer 1987;60:2117-22.

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CONTRACT IN SUPPORT OF OF THIS PROJECT

BIOLOGICAL RESEARCH FACULTY AND FACILITY, INC. (NOI-CP7-1025-00)

Title: Biological Specimen Repository for Patients at High Risk for Cancer

Current Annual Level: $193,450

Person Years: 2.05

Objectives: To maintain repository of fibroblasts and tumor cell lines, to grow to bulk culture selected cell lines, and to initiate new cell lines from individuals at increased risk of cancer.

Major Contributions:

The laboratory was sent 46 skin biopsy specimens to establish fibroblast lines. A total of 272 samples were dispersed to 16 destinations. Twenty-one cell lines were grown to 1/4 gm quantities. The cells grown to bulk are used to extract DNA for gene mapping studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04411-12 EEB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(50 characters or less. Title must fit on one line between the borders.)*

Cancer and Related Conditions in Domestic Animals: Epidemiologic Comparisons

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. M. Hayes	Veterinary Medical Officer	EEB	NCI
Others:	K. P. Cantor	Epidemiologist	EEB	NCI
	R. N. Hoover	Chief	EEB	NCI
	L. W. Pickle	Statistician	EEB	NCI
	B. Sass	Veterinary Medical Officer	OD,DCE	NCI

COOPERATING UNITS *(if any)*

Ohio State University (W Beard, R Stewart, R Schneider, P Constable)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Environmental Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.3	1.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The continuing purpose of this project is to identify domestic animal models applicable to further research into the etiology of cancer and related disease in humans. As cases accumulate, it is likely that some types of spontaneous cancers in pet animals can be identified as representing the effects of low-level environmental exposure to carcinogenic agents. The frequency of cancer in these animals would serve as a warning of general environmental hazard(s) to people in the same locale. The topics of current investigation are: 1) environmentally influenced cancer in dogs (e.g., bladder, nasal, and oral cancers); 2) the epidemiologic features of prostatic cancer in pet and military working dogs; 3) a case-control study of malignant lymphoma in dogs using owner questionnaires to assess household and yard chemical use; and 4) equine oncology and teratology.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

H. M. Hayes	Veterinary Medical Officer	EEB	NCI
K. P. Cantor	Epidemiologist	EEB	NCI
R. N. Hoover	Chief	EEB	NCI
L. W. Pickle	Statistician	EEB	NCI
B. Sass	Veterinary Medical Officer	OD,DCE	NCI

Objectives:

To investigate the distribution of cancer and related conditions in domestic animals in order to: 1) clarify etiologic factors in humans, 2) identify animal models useful in research, and 3) identify sentinels which may act as early predictors of environmental hazards to man.

Methods Employed:

Animals with the disease under investigation are identified from medical abstract records supplied to the Environmental Epidemiology Branch by participants in the Veterinary Medical Data Program. For comparison, a population-at-risk is constructed from patients seen by participants during the same time period under study. Relative risks for various factors (i.e., age, breed, sex, and various environmental variables) are calculated for the diseased animals. Other analytical techniques employed may include case-control comparisons for factors associated with disease in man. Other animals are studied whenever another resource is available (e.g., military working dog autopsy file of the Armed Forces Institute of Pathology).

Major Findings:

Canine Chemodectomas

A study of 279 dogs with an aortic body tumor (ABT), 67 with a carotid body tumor (CBT), and 11 with both tumors showed distant metastases, mostly to the lungs and liver, in 12% of the ABT cases and 16% of those with CBT. As in man, dogs experienced certain other concomitant neoplasms. These second primary tumors were more evident in dogs with ABT than CBT. The most frequent were thyroid carcinomas, interstitial cell tumors, and seminomas.

Canine chemodectomas typically have been considered as one disease irrespective of their primary site of occurrence or patient breed. The present study argues against this interpretation. Specifically, canine aortic body tumors are diagnosed at least 4 times more commonly than carotid body tumors. Secondly, English bulldog-related breeds (English bulldog, Boxer, Boston terrier, etc.) show a significant propensity for both ABT and CBT; no other pure breed was

detected with a statistically significant risk. Thirdly, a significant elevated risk in male dogs was evident among bulldog-related breeds but was not seen in other pure breeds. Lastly, bulldog-related breeds experienced more second primary tumors than other dogs, irrespective of the primary location of their chemodectoma.

Equine Gastrointestinal Carcinomas

A retrospective study of 250,000 horses seen in clinic identified squamous cell carcinoma (SCC) of the aglandular stomach as the most common gastrointestinal carcinoma (N=64). With the exception of man, spontaneous alimentary carcinomas are rare in monogastrics. Most of these cancers originate from glandular epithelium except in the rat and mouse, and the horse. The etiology of equine gastric SCC is unclear, but, based on experimental work with laboratory rats and mice, species whose gastric anatomy resembles that of the horse, several etiologic hypotheses are plausible.

Considerable bacterial fermentation of ingested food takes place in the aglandular equine stomach allowing it to be exposed to the reduction of ingested nitrates to nitrites and/or to the nitrosation of protein substrates (amines and amides) to form carcinogenic nitrosamines and nitrosamides. The source of the dietary nitrates may be feedstuffs themselves and/or nitrate contaminated water. N-nitroso compounds are broadly acting potent carcinogens capable of inducing malignancy throughout the gut. In the laboratory rodent, the incidence and sites of N-nitroso compounds given orally or by stomach tube typically induce gastric SCC, with and without accompanying glandular gastric carcinoma.

Another etiologic mechanism for equine gastric SCC may involve a reaction to feedstuffs or water contaminated with carcinogenic polycyclic aromatic hydrocarbons [e.g. benzo(a)pyrene]. Sometimes they are produced through biosynthesis or bacterial degradation, but more often they are produced through the inefficient combustion of carbonaceous materials. Some of these compounds are considered among the most carcinogenic components of polluted air. Carcinogenic polycyclics, when fed orally to mice or placed directly on the gastric mucosa of rats have been shown to induce aglandular SCC rather than carcinoma of the glandular stomach. This induction was greatly enhanced in rodents when the carcinogen was administered in the presence of mineral oil, a common substance routinely used as an equine purgative.

Weather Variables and Disease

A retrospective study of 8,975 dogs seen between 1975-1979 in North America found that dogs with pendulous ears and heavy ear canal hair had significantly more otitis externa than dogs with other ear-types. Regression analysis was applied to the prevalence data from individual veterinary treatment centers coupled with the monthly weather variables of mean temperature, rainfall, and relative humidity. The results provided evidence that variations in weather

explain substantial variations in the monthly hospital prevalence of first-diagnosed cases of canine otitis externa.

Feline Hip Dysplasia

A prospective pelvic radiographic study of 300 asymptomatic cats brought to veterinary attention for reasons other than mobility dysfunction or known skeletal abnormalities identified 30 with mild-to-severe hip dysplasia. A significant positive association was evident between body weight, incidence, and severity of the condition. There was no detectable familial risk.

Testis Tumors

A detailed review of reports of experimentally induced and spontaneous occurring testis tumors in laboratory and domestic animals identified affected species and strain/breeds. The array of tumor cell-types varied by species; those induced experimentally usually have been interstitial cell tumors, especially in laboratory mice and rats. Reports of testis tumors are uncommon-to-rare in domesticated animals. Farm animals, in particular, are most often castrated at a young age thereby removing them from the "at-risk" population. Of those tumors diagnosed in the horse, most are either seminomas or teratomas of the testis; rarely have interstitial cell or Sertoli cell tumors been observed. The domestic cat is another species about which only a few reports of testis tumors exist. The "pet dog" is the exception to the typical "castration" practice of domestic animals as he is often permitted to live his life sexually intact. Because of this, or possibly due to a species characteristic, canine testicular tumors are a common recognized occurrence. Seminomas, interstitial cell and Sertoli cell tumors occur with equal frequency, but do exhibit different age and breed susceptibilities. There is a paucity of reports of spontaneous testis tumors in wildlife and zoo animals. Interstitial cell tumor, seminoma, and Sertoli cell tumors have been reported in nonhuman primates. Considering the few opportunities to observe testis tumors in jungle cats and other "big" cats, reports of several cases suggest that these animals, as a group, may have a higher incidence than the domesticated cat.

Publications:

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Hayes HM, Pickle LW, Wilson GP. The effects of ear-type and weather on the hospital prevalence of canine otitis externa. Res Vet Sci 1987;42:294-298.

Hayes HM, Sass B. Chemoreceptor neoplasia: a study of the epidemiological features of 357 canine cases. Zentralbl Veterinarmed [A] (In Press)

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Hayes HM, Sass B. Testis neoplasia in captive wildlife mammals: comparative aspects and review. J Zoo Anim Med 1987;18:36-9.

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Hayes HM, Tennant BC. Squamous cell carcinoma of the stomach and other primary gastrointestinal carcinomas of the horse: case survey of North American university veterinary hospitals. J Am Vet Med Assoc (In Press)

Sass B, Hayes HM. Chemoreceptor neoplasia: comparative features in laboratory animals, domestic animals, and man. In: Kaiser HE, ed. Progressive stages of neoplastic growth, vol. 5. London: Alden Press, 1988;183-201.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04480-12 EEB

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies of Occupational Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. Blair	Chief, Occupational Studies Section	EEB	NCI
Others:	M. Dosemeci	Visiting Fellow	EEB	NCI
	M. Gomez	Industrial Hygienist	EEB	NCI
	R. Hayes	Epidemiologist	EEB	NCI
	E. Heineman	IRTA Fellow	EEB	NCI
	B. Miller	Epidemiologist	EEB	NCI
	P. Stewart	Industrial Hygienist	EEB	NCI
	S. Zahm	Epidemiologist	EEB	NCI

COOPERATING UNITS *(if any)*
Univ. of NE (D. Weisenberger); Univ. of NC (C. Shy); U.S. Coast Guard (T. Haas); USDA (J. Teske); U.S. Air Force (S. Birch); NIOSH (H. Amandus, W. Halperin, R. Herrick, K. Steenland); MO Cancer Control Program (R. Brownson)

LAB/BRANCH
Environmental Epidemiology Branch

SECTION
Occupational Studies Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
12.5	9.5	3.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Occupational Studies Section conducts epidemiologic studies to determine the role factors from the workplace play in the origin of cancer. Major areas of focus include pesticides, organic solvents and other widely used chemicals, and organic and inorganic dusts. Projects are underway to clarify the provocative associations between pesticides and certain cancers found in earlier Section studies. Cohort mortality studies of pesticide applicators employed by a national lawn care company and county noxious weed departments have recently been initiated. Results from a case-control study of lymphatic and hematopoietic cancer in Nebraska will be available shortly. Nasopharyngeal cancer was found to be associated with occupational exposure to formaldehyde in a case-control study, resembling findings from a mortality study of industrial workers. A study of embalmers is underway which includes a detailed industrial hygiene monitoring component for formaldehyde and other chemicals to clarify cancer excesses reported in this occupation. The 10-fold excess of astrocytic brain cancer associated with long-term employment in the electronics industry in a case-control study appeared to be more closely related to solvent and other chemical exposures than to electromagnetic radiation. Evaluation of the risk of bladder cancer among persons employed in the chemical industry using data from the National Bladder Cancer Survey found few significant excesses, although men employed for more than 20 years in the production of organic chemicals had a 2.4-fold excess. Major efforts underway include industrial workers exposed to acrylonitrile; grain millers exposed to fumigants; workers in dusty trades exposed to silica; workers in China exposed to benzene; firefighters exposed to combustion products; and furniture workers exposed to wood dusts, metal fumes, and paints, varnishes and solvents. Methodologic studies are being conducted to improve exposure assessment procedures and to develop resources for occupational studies such as a referent data base composed of workers.

PROJECT DESCRIPTION

Names, Title, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

A. Blair	Chief, Occupational Studies Section	EEB	NCI
M. Alavanja	Special Assistant	E&B	NCI
K. Cantor	Epidemiologist	EEB	NCI
J. Chandler	Biochemist	EEB	NCI
M. Dosemeci	Visiting Fellow	EEB	NCI
J. Fraumeni	Associate Director	E&B	NCI
M. Gomez	Industrial Hygienist	EEB	NCI
R. Hayes	Epidemiologist	EEB	NCI
E. Heineman	IRTA Fellow	EEB	NCI
R. Hoover	Chief	EEB	NCI
B. Miller	Epidemiologist	EEB	NCI
J. Sontag	Special Assistant	E&B	NCI
P. Stewart	Industrial Hygienist	EEB	NCI
S. Zahm	Epidemiologist	EEB	NCI

Objectives: The Occupational Studies Section conducts a comprehensive program of occupational studies to evaluate the role factors in the workplace play in the origin of cancer. The primary focus of this project is to identify and clarify the role that specific occupational factors play in the origin of cancer by integrating industrial hygiene evaluation into study designs.

Methods Employed: To accomplish this goal the Section conducts: a) descriptive and hypothesis-generating studies of occupations and industries to identify promising areas of research and to sharpen hypotheses, b) analytic studies with detailed industrial hygiene components to evaluate the carcinogenicity of specific occupational exposures, (c) industrial hygiene activities to evaluate workplace exposures and to improve methods of exposure evaluation in epidemiologic studies, and d) projects to improve epidemiologic methods and to develop resources for occupational studies.

Major Findings:

1. Cancer excesses have been noted in several groups exposed to pesticides. A twofold excess of leukemia was noted among agricultural extension agents from the U.S. Department of Agriculture who came into contact with pesticides while conducting demonstration projects for farmers. In a nested case-control analysis, the risk of lymphatic leukemia rose to 5.4 among those employed for 15 or more years. An interview case-control study in Iowa and Minnesota found associations between chronic lymphatic leukemia and non-Hodgkin's lymphoma among farmers using certain pesticides 20 or more years before interview. Significant associations occurred between chronic lymphatic leukemia and dichloro-diphenyl-trichloroethane (DDT) (OR=1.7), malathion (OR=2.4), dichlorvos (OR=2.2), and 2,4,5-T (OR=4.1), and between non-Hodgkin's lymphoma and DDT (OR=1.4), chlordane (OR=1.9), dieldrin (OR=4.9), lindane (OR=1.8), malathion (OR=2.2), carbaryl (OR=2.9), and chloramben (OR=2.6).

2. A case-control study in Connecticut noted an excess of nasopharyngeal cancer, but not sinonasal, among persons holding jobs where contact with formaldehyde may have occurred. Risks rose to over twofold among those with probable exposure to high levels 20 or more years prior to death. These results are consistent with an excess for this tumor seen in an earlier Section study of a large cohort of industrial workers exposed to formaldehyde.

3. A large case-control study of brain cancer (741 cases, 1266 controls) located in Pennsylvania, New Jersey, and Louisiana uncovered excess risks among persons employed in jobs in the electric and electronics industries (OR=2.3). Relative risks for astrocytic brain cancer rose with duration of employment in the manufacture or repair of electronic equipment to 10-fold among those employed for 20 years or more. No significantly elevated risks were associated with employment in the chemical industry (OR=1.2), although there were slight excesses among persons with exposure to cutting fluids (OR=1.6), organic solvents (OR=1.3), and those employed in the petroleum industry (OR=1.5).

4. The relationship between bladder cancer and employment in the chemical industry was assessed in a study of 2,982 incident cases and 5,782 population controls. Employment in the production of organic chemicals was associated with a 1.3-fold risk among men and the risk increased with duration of employment to 2.4-fold among those employed 20 or more years. Excesses were associated with employment in the plastics industry among women (OR=3.3) and among men holding a dusty job (OR=4.6). A slight excess among men in agricultural chemicals (OR=1.4) was attributable to risks in the pesticides subdivision (OR=2.3).

5. Monitoring of formaldehyde levels in several industries as part of an epidemiologic study found that current levels for jobs in manufacturing plants had geometric means that ranged from 0.03 to 1.88 ppm in summer and from 0.49 to 0.81 ppm in winter. Mean concentrations in plants manufacturing decorative laminates were generally below 0.60 ppm, in plywood plants below 0.40 ppm, and in photographic film plants below 0.50 ppm.

6. Occupational data from five case-control studies in the United States involving 2,973 male cases and 3,210 controls were analyzed to estimate the proportion of lung cancer attributable to well-known and suspected lung carcinogens. The proportion due to well-known occupational carcinogens ranged, by study area, from 3 to 17%. Further inclusion of occupational groups with exposures to suspected carcinogens changed these estimates very little.

Publications:

Alavanja MCR, Blair A, Merkle S, Teske J, Eaton B. Mortality among agricultural extension agents. Am J Industr Med (In Press)

Alavanja MCR, Malker H, Hayes RB. Occupational cancer risk associated with the storage and bulk handling of agricultural food stuff. J Toxicol Environ Health 1987;22:137-41.

Blair A, Cantor KP, Gibson R, Everett G, Shuman L, Burmeister L, Van Lier S, Blattner W. Lymphatic and hematopoietic cancer among farmers. In: Dosman J, ed. Proceeding of the international symposium on health and safety in agriculture. Boca Raton: CRC Press (In Press)

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Blair A, Dosman J, McDuffie H. Workshop on cancer in rural areas. Can Med Assoc J 1987;136:924-5.

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Brown LM, Mason TJ, Pickle LW, Stewart PA, Buffler PA, Ziegler RG, Fraumeni JF Jr. Occupational risk factors for laryngeal cancer on the Texas coast. Cancer Res (In Press)

Cantor KP, Blair A. Agricultural chemicals, drinking water and public health: an epidemiologic view. Proc Soil Sci Soc (In Press)

Cantor KP, Blair A, Everett G, Van Lier S, Burmeister L, Dick F, Gibson R, Schuman L. Hair dye use and risk of leukemia and lymphoma. Am J Public Health 1988;78:570-1.

Cantor KP, Blair A, Zahm SH. Agricultural chemicals, drinking water, and public health: an epidemiologic overview. J Contaminant Hydrology (In Press)

Connelly RR, Spirtas R, Myers MH, Percy CL, Fraumeni JF Jr. Demographic patterns for mesothelioma in the United States. JNCI 1987;78:1053-60.

Dick F, Van Lier S, Banks P, Frizzera G, Witrak G, Gibson R, Schuman L, Isacson P, O'Conor G, Cantor KP, Blattner W, Blair A. Use of the working formulation for non-Hodgkin's lymphoma in epidemiologic studies. JNCI 1987; 78:1137-44.

Hayes RB. Review of occupational epidemiology of chromium chemicals and respiratory cancer. Science Total Environ (In Press)

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Oishi K, Okada K, Yoshida O, Yomabe H, Ohno Y, Hayes RB, Shroeder FH. A case-control study of prostatic cancer with reference to dietary habits. Prostate (In Press)

Roush GG, Walrath J, Stayner LT, Kaplan SA, Flannery JT, Blair A. Nasopharyngeal cancer, sinonasal cancer and occupations related to formaldehyde. A case-control study. JNCI 1988;79:1221-4.

Schiffman MH, Pickle LW, Fontham ETH, Zahm SH, Falk R, Correa P, Fraumeni JF Jr. Diet and malignant mesothelioma: Evidence for a protective effect of vegetable consumption. Cancer Res (In Press)

Simonato L, Andersen A, Blair A, et al. Workshop on priorities for epidemiologic studies on occupational cancer. Scand J Work Environ Health 1987;13:74-5.

Simonato L, Fletcher A, Saracci R, Thomas TL, eds. Proceedings of the working group of the carcinogenic risk from exposure to silica. IARC Special Publication. Lyon, France: WHO (In Press)

Spirtas R, Connelly RR, Tucker MA. Survival patterns for malignant mesothelioma: The SEER experience. Int J Cancer (In Press)

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Thomas TL, Stewart PA, Stemhagen A, Correa P, Norman SA, Bleecker ML, et al. Risk of astrocytic brain tumors associated with occupational chemical exposures: a case-control study. Scand J Work Environ Health 1987;13:417-23.

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Vineis P, Thomas T, Hayes RB, Blot WJ, Mason TJ, Pickle LW, Correa P, Fontham ETH, Schoenberg J. Proportion of lung cancers in males due to occupation in different areas of the U.S. Int J Epid (In Press)

Vineis P, Zahm S. Immunosuppressive effects of dioxin in the development of Kaposi's sarcoma and non-Hodgkin's lymphoma. Lancet 1988;I:55.

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Zahm SH. Epidemiology of cancer among herbicide-exposed occupational groups. In: Heald RC, ed. Proceedings from the eighth annual forest management conference. Redding, CA: Forest Vegetation Management Conference, 1986;70-9.

Zahm SH, Blair A. Geographical differences in lymphoma incidence. Br J Cancer (In Press)

Zahm SH, Blair A. Cancer risk among agricultural workers exposed to herbicides in Kansas. In: Proceedings for the national conference on agent orange. William Joiner Center for the Study of War and Social Consequences. Boston, MA: University of Massachusetts (In Press)

Zahm SH, Hartge P, Hoover R. The national bladder cancer study: employment in the chemical industry. JNCI 1987;79:217-22.

Zahm SH, Liddell FDK, Frentzel-Beyme R. Combining data for epidemiologic studies with examples from occupational health. Public Health Rev (In Press)

CONTRACTS IN SUPPORT OF THIS PROJECT

ORI, INC. (NO1-CP-61039)

Title: Support Services to Develop a Computerized Comparison Population for Occupational Studies

Current Annual Level: $43,934

Person Years:: 1

Objectives: To assemble data from completed NCI and NIOSH cohort mortality studies and to develop a comparison population of workers for use in epidemiologic studies.

Major Contributions:

Completed cohorts from NIOSH and NCI have been received and have been arranged in a standardized format. Programs are being developed to construct matrices of reference rates that can be provided to investigators.

SRA TECHNOLOGIES, INC. (NO1-CP-41022)

Title: Mortality Study of Workers Exposed to Acrylonitrile

Current Annual Level: $285,000

Person Years: 2

Objectives: To provide data collection services for a cohort mortality study of workers exposed to acrylonitrile in eight plants.

Major Contributions:

A cohort of over 25,000 workers has been assembled from personnel records for the eight participating plants. Complete work histories have been abstracted and keyed. A ten percent sample of the cohort is being interviewed to obtain information on smoking. Tracing of study subjects is underway to determine vital status. Industrial hygiene monitoring has been conducted in each of the plants.

WESTAT, INC. (NO1-CP-51018)

Title: Support Services for Occupational Studies

Current Annual Level: $697,600

Person Years: 15

Objectives: To provide data collection and data management services for occupational studies. Activities include abstracting and interviewing, keying, coding, and editing of the data, monitoring and assessing occupational exposures, tracing study subjects, and performing statistical tabulations.

Major Contributions:

During the past fiscal year approximately 20 projects have received support under this contract. These have included projects such as case-control studies of lymphatic and hematopoietic cancer and pesticide exposure in Nebraska; of brain cancer and leukemia among embalmers, and lung cancer among pesticide applicators; and cohort mortality studies of lawn care workers, aerial applicators, firefighters, plumbers and pipefitters, dry cleaners, jewelry workers, chemists, shipyard workers, Coast Guard marine inspectors, and furniture workers. Support was also provided for a feasibility study of workers exposed to methylene chloride and preliminary exposure evaluation in funeral homes. Methodologic studies to improve and compare procedures used to estimate historical exposures were also supported.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05128-09 EEB

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Diet and Nutrition in Cancer Etiology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

PI:	R. G. Ziegler	Nutritional Epidemiologist	EEB	NCI
Others:	L. A. Brinton	Chief, ESS	EEB	NCI
	K. E. Brock	IRTA Fellow	EEB	NCI
	J. F. Fraumeni, Jr.	Associate Director	E&B	NCI
	R. N. Hoover	Chief	EEB	NCI
	C. J. Jones	Staff Fellow	EEB	NCI
	M. H. Schiffman	Clinical Investigator	EEB	NCI

COOPERATING UNITS *(if any)*
NCHS (H Barbano); NIA (J Huntley); CA Tum Reg (D West); Univ of HI (A Nomura); USC (B Henderson); Kaiser Hlth Plans (A Glass); Walter Reed Army Med Ctr (J Daniel); Beth Naval Hosp (A Robinson); GWU Hosp (L Smith); MN Med Res Cen (S Schwartz); Lipid Nut. Unit, USDA (PP Nair).

LAB/BRANCH
Environmental Epidemiology Branch

SECTION
Environmental Studies Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.2	0.3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Dietary exposures being assessed in human populations include consumption of specific food groups and food items, such as meat, fruits, and vegetables, ethnic dishes, and coffee; macronutrient and micronutrient intake, such as fat, vitamin A, carotenoids, vitamin C, folacin, and trace minerals; general nutritional status; anthropometry; biochemical indices, such as serum cholesterol and serum beta-carotene; and storage and cooking practices. Cancers being studied include those of the colon, rectum, breast, lung, cervix, and larynx. Case-control studies have been initiated in high risk areas with unusually high site-specific cancer mortality, conceivably related to diet, and among migrants whose changing cancer rates appear related to new life-styles, such as Asian-Americans. Analytic case-control studies of specific cancers have assessed nutrition and diet as possible risk factors, and studies of breast cancer and colorectal cancer that are primarily focused on diet have been developed. Selected cohorts with relevant dietary or biochemical data already collected, such as HANES I participants, are being followed for cancer morbidity and mortality. Data from HANES I are being analyzed to test specific hypotheses, and to provide descriptive information on U.S. dietary patterns, diet variation, and determinants of nutrient intake. Laboratory measures of nutritional status are being incorporated into selected case-control studies.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

R. G. Ziegler	Nutritional Epidemiologist	EEB	NCI
L. A. Brinton	Chief, ESS	EEB	NCI
K. E. Brock	IRTA Fellow	EEB	NCI
J. F. Fraumeni, Jr.	Associate Director	E&B	NCI
G. Gridley	Statistician (Health)	EEB	NCI
R. N. Hoover	Chief, EEB	EEB	NCI
C. J. Jones	Staff Fellow	EEB	NCI
C. Schairer	Statistician (Health)	EEB	NCI
M. H. Schiffman	Clinical Investigator	EEB	NCI
X. O. Shu	Visiting Fellow	EEB	NCI

Objectives:

(1) To assess in human populations specific hypotheses concerning the relationships of diet, nutrition and cancer that have been suggested by biochemical, animal, clinical, and epidemiologic studies. (2) To test systematically for the associations between diet and nutrition and specific cancers and to generate hypotheses about the nature of any relationships detected. (3) To develop and validate methods for nutritional epidemiology, including dietary questionnaires, pertinent laboratory measures and analytic approaches. (4) To develop and utilize national nutrition data resources. (5) To elucidate the basic biology of carcinogenesis through studying the influence of diet on cancer in human populations.

Methods Employed:

1. To evaluate the role of methylxanthines, the case-control study of breast cancer within the Breast Cancer Detection Demonstration Program (BCDDP), described in project Z01CP05526-02 EEB, incorporated questions on coffee, tea, colas, and chocolate drinks.

2. In the continuation of the follow-up activities within the BCDDP cohort, a dietary component has been added to the mailed questionnaire. This will enable a number of nutritional hypotheses to be tested. The interview also includes questions on physical activity, alcohol use throughout life, and changes in weight and relative weight.

3. When Asian women migrate to the U.S., their low rates of breast cancer rise toward American rates over several generations as they adopt a more Westernized diet. To assess dietary effects on breast cancer risk, a population-based case-control interview study was initiated among Asian-American women in Los Angeles, San Francisco, and Oahu. Approximately 800 Chinese, Japanese, and Filipino cases diagnosed during 1983-87 have been interviewed. The study population is limited to subjects 55 years or younger so that many of their mothers also can be interviewed about the subjects' early diet and life-style.

The influence of age at migration to the U.S. and non-dietary measures of acculturation on breast cancer risk will be analyzed. Several months after diagnosis and treatment, fasting plasma and 12-hour urines are being collected for hormone, lipid, and micronutrient determinations.

4. Although colorectal cancer mortality rates for white men and women are about 50% lower in the South than in the North, within the 11 Florida counties with high rates of in-migration from the Northern U.S., mortality curves parallel the mortality curves for other large Southern counties. A death certificate-based case-control study of colorectal cancer involving telephone interviews of next-of-kin of 1100 cases and 1341 controls was conducted in these Florida retirement counties to assess whether there is a rapid reduction in risk on migration to the South and to explore possible causes, such as diet or sunlight.

5. A two-year, methodologic case-control study of colorectal cancer and diet has been completed at Walter Reed Army Medical Center, Bethesda Naval Hospital, and George Washington University Hospital. The study focused on potential diet-related biochemical markers of colorectal cancer risk; namely, fecal mutagens, fecal bile acids, and fecapentaenes (a highly genotoxic class of fecal mutagens), as well as serum nutrient levels. Study subjects were repeatedly interviewed regarding recent diet; and multiple blood and stool samples were taken during diagnostic workup, surgery, and recovery.

6. A methodologic case-control study of colorectal cancer in relation to fecal bile acids and neutral steroids has been initiated, using 120 stored fecal samples from the fecal mutagen study described above.

7. A methodologic case-control study of colorectal cancer in relation to fecal occult blood has been initiated in collaboration with Dr. Samuel Schwartz, the developer of the HemoQuant assay. This assay quantifies hemoglobin-specific porphyrins, some of which may permit sensitive and specific screening assays for the detection of colorectal cancer. Two hundred selected stool samples are being tested from cases and controls with gastrointestinal and non-gastrointestinal conditions.

8. A multi-center case-control study of 500 women with endometrial cancer is underway. An equal number of community controls and women hospitalized for hysterectomy for benign conditions will serve as comparison subjects. The dietary interview is designed to measure intake of all major nutrients, with a special emphasis on fat. To explore the role of obesity, height, weight, relative weight, and physical activity at various ages are being ascertained, and anthropometric measurements taken. Blood samples will enable a battery of hormone assays to be conducted so that the interrelationships of obesity, diet, hormones, and cancer risk can be evaluated. In one particular study center, fat patterns will be further investigated in the cases and hysterectomy patients with a methodologic study of fatty acid profiles carried out on plasma, red blood cells, cheek cells, abdomen and arm aspirates, and surgical abdominal fat, and with serologic determinations of cholesterol, triglycerides, and lipoproteins.

9. In the population-based case-control study of ovarian cancer in Shanghai, described in project Z01CP05526-02 EEB, usual adult intake of common Chinese foods was quantitatively assessed.

10. A dietary component focused on micronutrients postulated to be involved in the etiology of cervical cancer was added to the U.S. case-control study of invasive and in situ cervical cancer, described in project Z01CP05526-02 EEB. Food frequencies and a history of vitamin supplement use were used to estimate the usual adult intake of carotenoids, vitamin A, vitamin C, and folacin. In addition, information was collected on the use of vitamin supplementation during pregnancies since folacin depletion may occur during pregnancy. To complement the dietary interview, blood samples were collected six months after completion of treatment to measure serum levels of retinol, carotenoids, tocopherols, vitamin C, folacin, and selenium and red blood cell folacin.

11. The case-control study of in situ cervical cancer conducted in Australia, and described in project Z01CP05526-02 EEB, included a quantitative food frequency questionnaire to assess carotenoids and retinol in the diet. Plasma levels of total carotenoids and beta-carotene were also measured.

12. A dietary component, with an orientation similar to that of the U.S. study, was part of the Latin American study of invasive cervical cancer, described in project Z01CP05526-02 EEB. The influence of diet, as well as serum levels of retinol, carotenoids, tocopherols, and folacin will be examined.

13. The population-based case-control study of vaginal and vulvar cancer, described in project Z01CP05526-02 EEB, contains a dietary section and laboratory component oriented toward the micronutrients and dietary patterns hypothesized to be involved in cervical cancer etiology.

14. Micronutrient assay methods for the blood samples collected in the U.S. cervical cancer study have been selected. In the process, a number of practical problems have arisen and are to be addressed in methodologic studies. In cooperation with the Centers for Disease Control, the stability of carotenoids, retinol, tocopherols, ascorbic acid (in meta-phosphoric acid), and folacin (in ascorbic acid) over time at -70^{o}C is being investigated, as is the stability of vitamin C and folacin prior to addition of the appropriate matrix. Total carotenoids, beta-carotene, and several other carotenoids will be measured so that their interrelationships and their relation to cervical cancer risk can be evaluated. Vitamin C will be measured in three ways so that oxidation to dehydroascorbic acid can be detected and quantified, and the ability of a new high performance liquid chromotography (HPLC) methodology to reverse oxidation can be evaluated. Serum and red blood cell folacin will be measured by both a microbiologic technique and a radiobinding assay.

15. Questions about usual adult frequency of consumption of beer, wine, and hard liquor were added to a population-based incident case-control study of lung cancer in six high-risk areas of New Jersey. Interviews were completed for 763 cases and 900 controls.

16. A large multi-center population-based case-control study of oral and pharyngeal cancer was initiated by the Biostatistics Branch. A total of 1065 cases and 1182 controls or their next-of-kin were interviewed with a food frequency questionnaire to assess intake of the major sources of carotenoids, vitamin C, and dietary fiber as well as the overall pattern of the diet.

17. Data were analyzed from a case-control interview study of malignant mesothelioma in Louisiana, which gathered information on usual diet and on lifetime occupational exposure to asbestos. Thirty-seven patients with malignant mesothelioma of the pleura or peritoneum were matched to controls according to age, sex, race, and factors related to case ascertainment.

18. In cooperation with the National Institute on Aging, other NIH Institutes, and the National Center for Health Statistics, we attempted to trace and re-interview, by proxy if necessary, the 14,407 adults examined 8-14 years earlier in National Health and Nutrition Examination Survey I (NHANES I). Hospital records and death certificates were collected. Approximately 93% of the cohort was successfully traced. To facilitate future use of this cohort, we incorporated into the re-interview 1) additional questions about the major risk factors for the common cancers not included in the original interview, and 2) an expanded dietary section to complement the single 24-hour dietary recall originally administered.

Major Findings:

Breast Cancer

In the case-control study of breast cancer and benign breast disease within the BCDDP, there was no evidence of a positive association between breast cancer and methylxanthine consumption, either past or recent. In fact, there was some suggestion of a negative association, particularly in women diagnosed after age 50.

In the case-control study of colorectal cancer in Florida retirement counties, preliminary results indicate that increasing years of Florida residence for migrants from the North are not associated with decreasing risk of disease. However, the younger the age at migration to Florida, the lower the risk of colorectal cancer in both men and women, with the risk of those migrating at 36 to 65 years of age and at 66 years or older being 1.3 and 1.7, respectively, compared to the risk of those migrating at ages younger than 36.

Results from the study of fecal mutagens, diet, and colorectal cancer show a striking decrease in fecapentaene excretion among cases compared to controls that cannot be explained by the effects of diagnostic workup or bleeding. An autopsy study showed that excreted values are equivalent to intra-caloric measurements. These results fail to support a genotoxic role for fecapentaenes in the etiology of colorectal cancer. Most mutagenicity in the 750 collected samples could be explained by fecapentaene content. Non-fecapentaene mutagens were rare, but slightly elevated in cases compared to controls.

In the case-control study of ovarian cancer in Shanghai, the risk of ovarian cancer increased with the intake of fat from animal sources, but not with fat

from plant sources. After adjustment for socioeconomic status and other ovarian cancer risk factors, women in the highest quartile of animal fat consumption had 1.8 times the risk of those in the lowest quartile. Vegetables, legumes, and vitamin C appeared protective, with those in the highest quartile of intake having an adjusted RR of 0.6 compared to those in the lowest quartile. The effects of vegetables and animal fat seemed independent of each other.

In the case-control study of in situ cervical cancer in Australia, women in the lowest quartile of carotenoid, vitamin C, or folacin intake had approximately twice the risk of those in the highest quartile, although the trend was significant only for vitamin C. Retinol intake was not predictive of risk. Among the food items, salad vegetables and fruit juices were the most protective. The levels of total carotenoids and beta-carotene in the plasma were both inversely associated with risk, with women in the lowest quartile of beta-carotene having 5 times the risk of women in the highest quartile.

In the case-control study of lung cancer among white men in New Jersey, the risk associated with drinking any type of alcoholic beverage compared to nondrinkers was minimal (RR=1.1). There was, however, evidence of an elevation in risk among beer drinkers, with the RRs for moderate-heavy drinkers being 1.5 - 1.6 after adjustment for smoking.

In the case-control study of oral and pharyngeal cancer, preliminary analysis suggests that fruit is protective, a finding that could not be explained by any of the specific nutrients examined. No other food groups or nutrients were consistently elevated or reduced among the cases.

In the case-control study of malignant mesothelioma of the pleura and peritoneum conducted in Louisiana, the cases reported less frequent consumption of homegrown produce, cruciferous vegetables (p=.005), and all vegetables combined. An estimate of carotenoid intake was also significantly lower among cases. This reduction in risk with vegetable intake for a non-epithelial tumor could not be explained by differential asbestos exposure.

The relationship of breast cancer to dietary fat, calories, cholesterol, and saturated, monosaturated, and polyunsaturated fats, as well as percent of calories from fat, was investigated in the NHANES I cohort. No significant differences in dietary fat or any related measures were evident between cases and non-cases when mean intakes were compared. However, in proportional hazards analyses, total fat and saturated fat intake were significantly associated with decreasing risk. Consideration of fat as percent of calories resulted in a weaker inverse relationship.

The relationship of anthropometric variables to risk of breast cancer was also examined in this cohort. Women who developed breast cancer were taller and had greater frame size (elbow width) than non-diseased women. However, body size defined by weight, relative weight, or skinfold measurements was not associated with increased risk. The positive association of stature and frame size to breast cancer risk suggests that early nutrition may play an etiologic role.

The relation between serum cholesterol and cancer was also examined in the NHANES I cohort. Men in the lowest cholesterol quintile had nearly twice the incidence and mortality of those in the highest quintile. Among women a similar relation was seen for cancer mortality, but not for cancer incidence. The inverse cholesterol-cancer relationship in men was present for determinations made 6 or more years before cancer diagnosis, suggesting that lowered serum cholesterol may not simply be a result of preclinical disease. Analysis by site revealed inverse associations for cancers of the lung, rectum, bladder, and pancreas (but not colon) among men; and for cancers of the lung, bladder, pancreas, and cervix and leukemia (but not colon) among women. Thus, lowered cholesterol as a risk factor was primarily restricted to smoking-related cancers, a finding that persisted after adjustment for smoking.

Publications:

Brock KE, Berry G, Mock PA, MacLennan R, Truswell S, Brinton LA. Nutrients in diet and plasma and risk of in situ cancer. JNCI (In Press)

Brown LM, Mason TJ, Pickle LW, Stewart PA, Buffler PA, Burau K, Ziegler RG, Fraumeni JF Jr. Occupational risk factors for laryngeal cancer on the Texas Gulf Coast. Cancer Res 1988;48:1960-4.

Jones DY, Schatzkin A, Green SB, Block G, Brinton LA, Ziegler RG, Hoover R, Taylor PR. Dietary fat and breast cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. JNCI 1987;79:465-71.

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Schatzkin A, Hoover RN, Taylor PR, Ziegler RG, Carter CL, Larson DB, Licitra LM. Serum cholesterol and cancer in the NHANES I Epidemiologic Followup Study. Lancet 1987;ii:298-301.

Schatzkin A, Hoover RN, Taylor PR, Ziegler RG, Carter CL, Albanes D, Larson DB, Licitra LM. Site-specific analysis of total serum cholesterol and incident cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Cancer Res 1988;48:452-8.

Schiffman M.H. Diet and fecal genotoxicity. Cancer Surv (In Press)

Schiffman M.H. Bitterman P, Viciana A, Schairer C, Russell L, Van Tassell RL, Wilkins TD. Fecapentaenes and their precursors throughout human bowel: results from an autopsy study. Mutation Letters (In Press)

Schiffman MH, Pickle LW, Fontham E, Zahm SH, Falk R, Mele J, Correa P, Fraumeni JF Jr. A case-control study of diet and mesothelioma. Cancer Res (In Press)

Schiffman MH, Van Tassell R, Robinson A, Smith L Daniel J. Recent results regarding fecal mutagenicity. [Letter to the Editor]. Am J Epidemiol (In Press)

Taylor P, Schiffman MH, Jones DY, Judd J, Schatzkin A, Nair PP, Van Tassell R, Block G. Relation of changes in amount and type of dietary fat to fecapentaenes in premenopausal women. Mutation Res (In Press)

Ziegler RG. Epidemiology studies of carotenoids and cancer. J Nutr (In Press)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05400-05 EEB

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Epidemiology of Human Lymphotrophic Viruses: ATL, AIDS and Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)(Name, title, laboratory, and institute affiliation)*

PI:	W.A. Blattner	Chief, Viral Epidemiology Section	EEB	NCI
Others:	R.J. Biggar	Coordinator, International AIDS	EEB	NCI
	J.J. Goedert	Coordinator, AIDS Working Group	EEB	NCI
	S.Z. Wiktor	Medical Staff Fellow	EEB	NCI
	E.L. Murphy	Medical Staff Fellow	EEB	NCI
	A. Manns	Biotechnology Fellow	EEB	NCI
	P.H. Levine	Senior Investigator	EEB	NCI
	G. Agius	Guest Researcher	EEB	NCI

COOPERATING UNITS *(if any)*
U.W. Indies, Kingston (W.N. Gibbs); Caribbean Epidemiology Centre (C. Bartholomew); Gorgas Mem. Inst. Panama (W. Reeves); Biotech Labs (A. Bodner); Westat, Inc. (S. Durako); NICHD (A. Willoughby)

LAB/BRANCH
Environmental Epidemiology Branch

SECTION
Viral Epidemiology Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
11	10	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Human retroviruses are emerging as etiologic agents of human malignancies. Human T-lymphotrophic virus-I (HTLV-I) is linked to adult T-cell leukemia (ATL). Human immunodeficiency virus, (HIV, formerly HTLV-III/LAV) the etiologic agent of the acquired immunodeficiency syndrome (AIDS), is associated with Kaposi's sarcoma and certain forms of Hodgkin's and non-Hodgkin's lymphoma. Our research is focused on characterizing the relationship of this class of virus to human malignancy. Results of our studies document the spectrum of ATL and modes of spread of HTLV-I by heterosexual and homosexual contact and suggest early life transmission in the household. An indirect etiologic mechanism of carcinogenesis is also suggested for HTLV-I in B-cell chronic lymphocytic leukemia (B-CLL), and for HIV in studies of Hodgkin's and non-Hodgkin's lymphoma and Kaposi's sarcoma. A major focus of HIV research has been on cohorts at high-risk for AIDS followed longitudinally since the very beginning of the AIDS epidemic. Results for studies have documented major modes of transmission of HIV in homosexual men, in hemophiliacs, in drug users and their heterosexual partners, and from mother to offspring. The natural history of progression, the predictors and risk, and the incidence of various outcomes have been defined. Low T-helper cell counts are predictive of AIDS risk and may contribute to heightened transmission of HIV. Among various cofactors, an immunogenetic marker appears to be associated with heightened AIDS risk. Studies are also ongoing to utilize epidemiologic approaches to search for persons infected with related viruses and to search for etiologic relationships (e.g., HTLV-II and mycosis fungoides). With the recent discovery of human B-cell lymphotrophic virus (HBLV) (also known as human herpes virus - 6) our interest in DNA tumor viruses has also been revitalized. In particular, biochemical epidemiologic studies to investigate the possible role of oncogenic DNA viruses in HIV-1 related malignancies are planned.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliation of Professional Personnel Engaged on this Project:

W. A. Blattner	Chief, Viral Epidemiology Section	EEB	NCI
R. J. Biggar	Coordinator, International AIDS	EEB	NCI
J. J. Goedert	Coordinator, AIDS Working Group	EEB	NCI
D. L. Mann	Chief, Biochemical Epidemiology Section	LHC	NCI
R. C. Gallo	Chief	LTCB	NCI
E. Murphy	Medical Staff Fellow	EEB	NCI
S. Wiktor	Medical Staff Fellow	EEB	NCI
A. Manns	Biotechnology Fellow	EEB	NCI
R. N. Hoover	Chief	EEB	NCI
P. H. Levine	Senior Investigator	EEB	NCI
E. Maloney	Statistician	EEB	NCI
D. Reidel	Epidemiologist	EEB	NCI
G. Agius	Guest Researcher	EEB	NCI
A. Kraemer	Guest Researcher	EEB	NCI

Objective:

The objective of the Viral Epidemiology Section is to generate and test hypotheses concerning the role of pathogenic human viruses in the etiology of cancer and to expand our knowledge of the AIDS epidemic, with a particular focus on cancer.

Methods Employed:

Studies undertaken by the Viral Epidemiology Section involve a series of research approaches. Cross-sectional surveys and descriptive case series are employed to provide initial information on the distribution of virus exposure and the nature of related diseases. A major tool for analysis in the prospective cohort study which provides information on the natural history of infection, the frequency of disease occurrence resulting from exposure and the cofactors which modify risk. To analyze specific risk factors, case-control studies are employed defined on the basis of risk factors for infection on outcome. A variety of biochemical markers are utilized to define intermediate outcomes or markers of high risk.

Major Findings:

PROJECT 1: Human T-cell Lymphotrophic Virus-I (HTLV-I)

The discovery of the first human retrovirus, HTLV-I, by the Laboratory of Tumor Cell Biology (LTCB) of the NCI has given new impetus to the hypothesis that viruses cause human cancers. The objective of this project is to undertake a series of epidemiologic, clinical, and experimental studies aimed at defining the epidemiology of HTLV-I infection and its role as a cause of human cancer.

To accomplish this objective, the Viral Epidemiology Section of the Environmental Epidemiology Branch has developed a series of projects in the United States and internationally to explore etiologic relationships between HTLV-I and leukemia and lymphoma. A major thrust of these activities are a series of analytic epidemiologic studies focusing on various diseases thought to be linked to HTLV-I and on populations at risk for HTLV-I infection. To support these activities, a series of research contracts have been established with the University of West Indies at Kingston, Jamaica; the Caribbean Epidemiology Research Center, Port-of-Spain, Trinidad; Gorgas Memorial Institute, Panama City, Panama; and the Kuakini Medical Center in Honolulu, Hawaii.

Adult T-cell Leukemia

A case-control study of adult T-cell leukemia (ATL), established in Kingston, Jamaica in January 1984 and in Port-of-Spain, Trinidad in February 1985, completed enrollment of over 100 cases of ATL in February 1988. Preliminary analysis has documented a 35-fold increase in risk for ATL among persons seropositive for HTLV-I. Of note is the observation that close to 20% of incident cases with features of ATL were antibody negative. A current thrust of this project is to apply new tissue typing approaches to clarify the T-cell phenotype of cases. In addition, the technique of polymerase chain reaction will be applied to search for virus-positive, antibody-negative ATL cases.

The molecular analysis of Jamaican non-Hodgkin's lymphoma cases of HTLV-I virus utilizing conventional molecular hybridization approaches documented the presence of integrated HTLV-I viral DNA in all antibody-positive cases and its absence in negative cases. In Jamaica, the incidence of ATL is calculated to be approximately 4 per 100,000 per year in the population over the age of 30. Male and female rates are similar and the pattern of disease in relationship to age-specific infection rates suggests that early life exposure is most important for subsequent risk for ATL.

Surveys of adult non-Hodgkin's lymphoma to search for HTLV-I-associated ATL have been undertaken in several geographic locales. In the United States, an ATL registry has been developed for categorizing cases previously identified, to enroll new cases referred to the NCI for evaluation, and to record features of cases reported in the literature. Among the first 74 cases, the previously identified pattern of U.S. cases was confirmed. Specifically, ATL occurs among persons of African ancestry, either born or with links to the southeastern U.S., or among migrants to the U.S. from viral endemic areas of the world, particularly the Caribbean basin and southern Japan. A "cluster" of 16 ATL cases that was recently investigated in Brooklyn, New York, among a predominantly black population with links to the southeastern U.S. or Caribbean basin supported the long latency between infection and disease outcome. Surveys in Panama and Colombia, South America, have documented a paucity of cases despite elevated rates of seropositivity in the population at risk. In Colombia, cases cluster among persons of African ancestry residing in the low altitude, high rainfall coastal region. The cases in Panama share common features with ATL from the region, but the proportion is much lower than that

reported from Jamaica and Trinidad. Surveys in other areas suspected to have significant HTLV-I seroprevalence are underway in Ghana, Nigeria, and Papua, New Guinea.

Tropical Spastic Paraparesis

Recently, a link of HTLV-I to a demyelinating neurologic condition, tropical spastic paraparesis (TSP), has been reported. In conjunction with collaborators from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Jamaican and Trinidadian collaborators, we are initiating an analytic case-control study of TSP utilizing a questionnaire patterned after our questionnaire utilized to study ATL. This parallel study seeks to define similarities and differences between TSP and ATL which may provide clues to latency and risk factors for these HTLV-I-related diseases. As part of this protocol, we are evaluating the hypothesis that different immunogenetic factors predispose to these diseases. In Panama, incident cases of TSP are being ascertained nationwide to define the relative frequency of occurrence compared to ATL incidence and to define clinical features.

Foodhandler Study

In Jamaica, the cross-sectional seroprevalence survey of 13,500 food service employees (foodhandlers) is the mainstay of our future targeted epidemiologic studies. Analysis of these data was delayed while our HTLV-I testing was upgraded but is now complete and manuscript preparation is in progress. The major findings include: a) a marked female excess in prevalence for all adult age groups; b) generally uniform geographical distribution of HTLV-I prevalence across the island of Jamaica, except for higher elevation; c) when age is controlled, there is no association between a woman's parity (cumulative number of pregnancies) and her likelihood of being seropositive; and d) a cluster of seropositive females was found at a single citrus juice factory. Further investigation is ongoing. These data have contributed to a manuscript which models the role of early life infection as the relevant exposure for subsequent adult risk of ATL. The seroprevalence rate of HIV-1 in this cohort was 0.4%.

Phase two of the foodhandler survey is a nested case-control study of risk factors for seropositivity. Two hundred fifty healthy seropositives were frequency-matched by age, sex, and locale of current residence with an equal number of seronegatives. Trained research nurses administered a detailed questionnaire modeled after the ATL case-control questionnaire covering medical and sexual history, residence, occupation, diet, and life-style. Blood and stool specimens were obtained for blood smear, serology, lymphocyte preservation, and examination for ova and parasites. In addition, a physical examination designed as a screening tool for ATL and TSP was performed by the nurses. Begun in January 1987, the field component of this phase is now complete. Of interest is the fact that among the first 150 seropositives to be screened, five had neurologic symptoms or signs, and one of these has been confirmed as a case of TSP.

Hepatitis Cohort

In Trinidad and Tobago, an occupationally-based cohort of 1,729 persons had been assembled for a study of hepatitis prevalence in 1982. Seroprevalence was higher on the small island of Tobago (11/151=11.9%) than on the larger island of Trinidad (35/1,575=2.2%). The use of an outdoor water supply and an outdoor toilet were both correlated with HTLV-I seropositivity on Tobago, suggesting that lower socioeconomic status may be linked to the higher rates on the small island. HTLV-I seropositivity was correlated with the presence of antibodies to hepatitis-B, which appeared to be a surrogate for male-to-female sexual transmission.

Barbados Cohort

In 1972, sera were collected by Dr. Alfred Evans (Yale University) in a population-based household survey of two health districts in Bridgetown, Barbados. We recently tested sera from this collection for HTLV-I. Overall, HTLV-I prevalence was 4.3% (43/1,012), with an age-specific increase and higher rates in females (5.7%) than in males (2.2%). The age-dependent rise in seroprevalence has a pattern identical (but at a lower rate) to the curve observed in the foodhandler survey in Jamaica, arguing that the age-dependent rise is not a result of a cohort effect since we would have expected higher rates to have been shifted to a younger age stratum in the 1972 survey. Data on results from the fluorescent treponemal antibody (FTA) test for syphilis were available for the cohort. A stronger correlation between positive FTA and antibodies to HTLV-I was observed for females (odds ratio=4.1, 95% CI=1.7, 9.7) than for males (odds ratio=2.6, 95% CI=0.5, 13.8). This is evidence in favor of preferential sexual transmission from males to females rather than from females to males. Perinatal transmission of HTLV-I was suggested by household clustering of antibody and the fact that seropositive children were more likely to have seropositive mothers than seronegative children, a pattern that was reported from Japan. There was no evidence in support of vector-borne transmission. We plan to reevaluate this 16-year-old cohort with questionnaires, blood samples, and physical examinations during 1989 to address the important issues of interval seroconversion and disease outcome.

Japan-Hawaii Cancer Study Cohort

Serologic analysis of a cohort of Hawaiian men from the Japan-Hawaii Cancer Study showed that rates and titers were highest in age-matched lifetime residents of Okinawa (35%), while the rates in Japanese-born migrants (issei) (20% seropositive) and first generation Hawaiian-born offspring of immigrants (nisei) (19% seropositive) were equal, although titer values compared to lifetime residents of Okinawa were intermediate for the issei and low for the nisei. A study to follow back to this cohort is ongoing. Preliminary data suggest that rates of infection may be falling off in the next U.S.-born generation, an association being evaluated by an analytic case-control study. Genetics may also play a role. Our collaborators in Hawaii have recently identified a second member of the cohort who has developed ATL. These cases

are seropositive brothers who were diagnosed with ATL seven years apart and whose documented antibody positivity antedated their development of ATL by 7 to 15 years.

Sexual Transmission

Sexual intercourse was postulated to be an important mode of transmission of HTLV-I by Japanese investigators early in the epidemiological investigations of the virus.

The prototype of our studies of sexual transmission had its field phase in Jamaica during the summer and fall of 1986. Two thousand sequential patients at sexually-transmitted disease (STD) clinics in Kingston and Montego Bay were enrolled when they presented for a new episode of STD. Serum and questionnaire data on sexual behavior were obtained from all subjects. Testing of the serum for HTLV-I and HIV by enzyme-linked immunosorbent assay (ELISA) and Western blot, data entry and editing lasted for most of 1987. Thus, data analysis has just begun. Preliminary results reveal HTLV-I prevalence of 3.2% in males and 8.5% in females. After adjusting for age, the female prevalence was significantly greater than that of female foodhandlers who are felt to be more representative of the general population. Correlation with questionnaire data and with serologic markers of other STDs is in progress.

In Trinidad, the pilot phase (serum and locator information only) of a study of heterosexual patients at the local STD clinic has been completed. It was initially intended to be similar to the study in Jamaica, but the finding of higher prevalence against HIV (23/747, or 3%) than against HTLV-I (15/747, or 2%) in the Trinidad STD clinic population has led us to reevaluate our approach. First, we need to ascertain by means of follow-up interviews that the HIV seropositives were indeed exclusively heterosexual. If this is the case, then screening of an additional 2,300 patients, followed by a nested case-control or case-contract study of HIV risk factors in this heterosexual group, is planned.

We have also undertaken studies of homosexual and bisexual men in both Trinidad and Jamaica. In Trinidad, HTLV-I and HIV seroprevalence rates were 15% and 40%, respectively, compared to 2.4% and 0.19% in a more general population survey. In Jamaica, HTLV-I and HIV seroprevalence were 5% and 10%, respectively, compared to 3% and 0.1%, respectively, in the foodhandler cohort. The studies found evidence that the high HTLV-I prevalence among these males was due to transmission by homosexual intercourse, and that duration of homosexuality, number of sexual partners, and history of gonorrhea infections were risk factors. In contrast, the strongest risk factor for HIV infection was sexual contact with American men. The risk factors usually associated with HIV infection in U.S. homosexual men were more difficult to detect, due in part to the small numbers of seropositives in these two studies. A follow-up of the 1983-84 Trinidad homosexual cohort for HIV and HTLV-I seroconversion, and for incidence of AIDS, is now underway. Preliminary data suggest that men co-infected with both viruses are at greater risk of developing AIDS.

We have also examined the hypothesis that homosexual men in the U.S. have an elevated prevalence of HTLV-I. One-thousand two-hundred seventy-nine sera from the Los Angeles site of the Multicenter AIDS Cohort Study (MACS), plus 316 sera from homosexual men in New York City, Washington D.C., or Hawaii, were tested forHTLV-I antibodies. Only one man (0.06%) was seropositive, suggesting that HTLV-I has not been introduced into these groups.

In a study of U.S. military personnel who had been based in Japan and Okinawa, 15 of 400 (3.8%) were seropositive for HTLV-I and risk correlated with duration of residence in Okinawa, reminiscent of the case of a Caucasian merchant marine with ATL from Massachusetts. Further analyses are underway, and we are planning to collaborate in a study funded by the Department of Defense aimed at following up on these preliminary findings.

Maternal to Child Transmission

Data collection has been completed on two preliminary surveys of maternal-infant HTLV-I transmission in Jamaica through collaboration with the Department of Child Health of the University of West Indies. Serial serum samples were collected from 600 infants for a study of measles vaccination efficacy. Testing for HTLV-I antibodies has revealed 7 HTLV-I-positive children. Family studies of the 7 seropositive and 14 matched seronegative children revealed that all positive children have seropositive mothers. In another retrospective pilot study in Kingston, Jamaica, 74 HTLV-I-positive pregnant females and their offspring are being studied to determine the frequency of HTLV-I antibodies among their offspring. Of all offspring of seropositive mothers, approximately 20% appear to be seropositive.

The estimates of transmission rates obtained from these studies will be used to plan a prospective cohort study of HTLV-I positive pregnant women and their offspring in Jamaica during 1989. The objective will be to ascertain the route of transmission, specifically the role of breast-feeding, and to identify the immunologic effects of perinatal HTLV-I infection.

Transfusion Transmission of HTLV-I

The Jamaican Blood Transfusion Service, sponsored by the Ministry of Health, serves as the major source of blood and blood products for the country of Jamaica. Over 54% of the island's blood originates from the Service's Main Center in Kingston, with 12,000 units collected per year. This center serves as the site of donor screening for this study, and recipients of blood units are in-patients at Kingston urban hospitals. All consecutive donors at the Main Center and University of the West Indies Hospital are screened for HTLV-I antibody by the NCI laboratory in Frederick, since no screening capability currently exists on-site in Jamaica and no assay has been licensed for clinical application. Pre-transfusion specimens are frozen for later analysis. In cases where blood units are not intercepted before transfusion, recipient pre- and post-transfusion samples are screened. Individuals with positive pre-transfusion samples will continue to be followed to evaluate the effect of re-exposure on antibody titer, although they will be analyzed separately from the

study focusing on seroconversion. Controls, matched to newly exposed cases by age, sex, and hospital, who received negative donor blood during the period of the study are being followed in an identical fashion. Serial serum samples and questionnaire data will be collected on a monthly basis for at least six months following transfusion.

Screening of blood donors commenced on May 29, 1987. As of December 1, 1987, 7,704 donors have been screened. Two hundred one positive donor units have been identified for a seroprevalence of 2.6%. Total enrollment of eligible recipients of positive units and recipient/controls approaches 100, with 50 in each group. Completion of the desired enrollment goal will be completed in early January 1988. Approximately 15% of the recipient cohort have completed four monthly interval visits. All have had index visits and 68% have had at least one monthly interval visit. A minimum of 45% of recipients of HTLV-I-positive blood units have seroconverted after a median time of 50 days. No recipients of negative blood units have seroconverted.

HTLV-I in Drug Abusers

Sera drawn in 1981-82 from parenteral drug abusers in Queens, New York, were examined for HTLV-I and HIV antibodies. Blacks were more likely than whites to be seropositive. Of 37 blacks, 46% had antibodies to HTLV-I or HTLV-II, whereas of 19 whites, 11% had such antibodies. Studies to further elucidate the significance of these findings have been initiated with questionnaires administered and sera collected in Queens, New York, six cities in New Jersey, New Orleans, Louisiana, and the District of Columbia. In New Orleans 45% of black drug abusers were HTLV-I seropositive, while in New Jersey rates of HTLV-I varied geographically with highest rates closest to the New York City area. Rates were higher in black than in non-black drug abusers, and rose with age.

PROJECT 2: HIV and AIDS

AIDS and Cancer

Using the Surveillance, Epidemiology and End Results (SEER) system, we have monitored cancer risk in single, young men through 1985, confirming an association with Kaposi's sarcoma and quantifying the link to Hodgkin's and non-Hodgkin's lymphoma. Hepatoma was also increased in frequency beyond that expected. In 1987, we initiated studies using the same approach in New York State, reasoning that New York City would have a "sentinel" population that was HIV-infected early and numerically large.

Preliminary review revealed that AIDS emerged in New York City by 1977, on the basis that AIDS-related Kaposi's sarcoma cases occurred then but not earlier. Several of these cases were still alive in 1987, and we are trying to obtain permission from New York State to interview these subjects and draw samples from them. In addition, analysis of the New York City data, still incomplete, suggests that an excess of Kaposi's sarcoma and non-Hodgkin's lymphoma is present among the AIDS-risk population of this city, and the profile was similar to the excesses found in San Francisco.

Studies are ongoing in Kaposi's sarcoma. We are now extending virologic studies to focus on a form of Mediterranean Kaposi's sarcoma in Greece, hoping to find a virus that may play a role in this malignancy. Additional sources of sera and cells from Kaposi's sarcoma are being sought from sources in the Mediterranean area and from doctors with access to HIV-negative (non-AIDS-related) cases in the United States.

Male Homosexual Cohorts

We continue to follow the progression of immunodeficiency among HIV-infected homosexual men. The analysis in progress confirms that few, if any, HIV-infected subjects will remain unaffected by this virus. Among our seroconverting subjects, all have had inverted helper-to-suppressor ratios by 40 months. Adding to our previous data on cofactors we identified immunogenetic markers of high risk and confirmed that antigenemia and urine neopterin also are useful markers of risk.

Hemophiliacs and Their Female Sexual Partners

In late 1982, a cohort of 85 hemophiliac patients was established and followed prospectively using stored serum samples from cohort members dating back to the mid-1970s. We have demonstrated that the earliest HIV seroconversion occurred in 1979, and that the majority of hemophiliacs seroconverted during 1981 and 1982. Six-year AIDS incidence after seroconversion is 18% $\pm$ 7%, and we have recently reported that after standardization of the cohort to individual seroconversion dates, low (<300 cells/ul) and especially very low (<150 cells/ul) T-helper counts predicted AIDS up to 12 months in advance. T-helper counts were decreasing much more rapidly in those hemophiliacs who have gotten AIDS (-29 cells/month) than in those who have remained AIDS-free (-6 cells/month). Older age (over age 21) and thrombocytopenia also appeared to increase the risk of AIDS.

Prior to the discovery of HIV, we showed that high levels of alpha interferon heralded the onset of AIDS by three to nine months in three hemophiliacs. A cohort of nearly 1,000 hemophiliacs was established at seven hemophilia treatment centers, and we have recently confirmed that detection of serum interferon predicted AIDS in 12 additional hemophiliacs. The possibility that this assay adds predictive value to T-cell testing is being analyzed, as are leads generated from the first cohort, such as thrombocytopenia and older age. Less common outcomes in this large cohort, such as lymphoid malignancies and Kaposi's sarcoma, are also being vigorously pursued.

In 1984, a small cohort of female sexual partners of the adult hemophiliacs was established. No HIV seropositive women were found during the first two years. In 1986, however, six women were found to have HIV antibodies, including three from the original cohort with documented seroconversions after more than four years of sexual contact with a seropositive hemophiliac. Detailed questionnaire data were unrevealing, but there was a strong association with extremely low T-helper counts (<100 cells/ul) in the seropositive male, suggesting that greatly increased infectiousness may occur as immunity rapidly

deteriorates. These data are being pursued in a cohort of some 200 female sexual partners recruited at eight hemophilia treatment centers.

Parenteral Drug Users

In 1982, 35 parenteral drug users from a methadone detoxification program and 35 parenteral drug users hospitalized for soft-tissue infections in New York were characterized immunologically and clinically. Analysis of sera from 1982 indicates significant serologic reactivity for antibodies to HTLV-I, -II, and HIV. The rates of HTLV-I and -II seropositivity, while controlling for race and HIV status, were higher in the soft tissue infection group compared to the detoxification group, suggesting a possible role of HTLV-I and -II in the development of immune deficiency states. Our Section is now engaged in following these study participants as part of a longitudinal cohort study. Two HIV-seropositive detoxification program individuals are known to have died of AIDS, one of whom was missed until Section staff had postmortem specimens reviewed at the Armed Forces Institute of Pathology.

In New Jersey, the AIDS case distribution is geographically clustered about the Jersey City/Newark/New York City epicenter. Under the leadership of Dr. Stanley Weiss, the Family Studies Section designed and completed a seroepidemiologic study of nearly 1,000 parenteral drug users in New Jersey to examine risk factors for HIV exposure, in collaboration with the National Institute on Drug Abuse (NIDA) and the New Jersey State Department of Health (NJSDH). Analyses indicate (1) a parallel between HIV and AIDS distribution; (2) that more frequent parenteral drug use in the preceding year was significantly associated with a higher rate of HIV seropositivity; (3) in multiple regions, blacks were more likely than whites to be HIV-seropositive, which parallels observational data on the geographic and racial distribution of AIDS cases in New Jersey; (4) persons enrolled longer in treatment programs were less likely to be seropositive; and (5) female drug abusers were as likely as males to be seropositive. The cohort is being prospectively evaluated for the development of AIDS, including periodic follow-up, as well as matching by NJSDH against their AIDS registry. During the first year of follow-up, three seropositive subjects (0.9%), and no seronegative subjects developed AIDS. In 1985, about 350 subjects who were still enrolled in treatment programs were retested for HIV antibodies. Seven of the 220 seronegatives seroconverted (4.1% annual rate).

Laboratory Workers Study

The Family Studies Section (FSS) has been conducting a serologic assessment of HTLV-I exposure among Laboratory of Tumor Cell Biology and FSS workers in an ongoing fashion. With the discovery of HIV, testing for this agent was undertaken as well, and the study was expanded to other research and retrovirus commercial laboratories. One worker has been found to be HIV-positive and was proven to be infected with a strain of virus being grown in the laboratory. No source of infection was identified, although inapparent contamination may explain the infection. A paper concerning this study reported that risk of infection approximates that among health care workers with documented

parenteral inoculation. Based on this report, guidelines for worker safety have been revised and a new HIV Agent Summary Statement issued the Public Health Service.

Mothers and Infants

A multidisciplinary study, in collaboration with the State University of New York Health Science Center in Brooklyn and the Albert Einstein College of Medicine of Yeshiva University in the Bronx, New York, funded in part by the National Institute of Child Health and Human Development, has been initiated to evaluate risk factors and natural history of HIV infection in pregnant women and their offspring. Pregnant women are enrolled in special clinics for drug abusers or Haitians and are interviewed and tested for HIV antibodies. Seropositive and seronegative women and their offspring are evaluated at frequent intervals with standardized clinical parameters, immunologic assays and (for the babies) neurodevelopmental tests.

Analysis of the data concerning immunological changes during pregnancy showed a consistent pattern of rising CD4 cells just prior to delivery. HIV-positive women had similar changes but generally lower CD4 and higher CD8 levels than HIV-negative women. The CD4 decline appeared to be faster in pregnancy than in the postpartum period, suggesting that pregnancy may accelerate immunodeficiency. No markers helped to identify which HIV-positive women were likely to infect their infants. Nor did we find immunologic markers in HIV-infected infants who were truly infected. However, generally, HIV-infected infants had low CD4 and high CD8 cells prior to the fourth to the sixth month of age. These studies are still in progress.

Global AIDS and HIV-Infection

We have reviewed the published data about AIDS and HIV prevalence and incidence from around the world. In general, most of the studies have had biases, some gross and others subtle, that impair their accuracy or limit the ability to generalize the conclusions. Furthermore, a major source of error is that the size of the risk groups themselves is unknown. This is particularly true of homosexual men, intravenous drug abusers, and sexually active heterosexuals, groups of major importance to describing the magnitude of the AIDS problem. Our estimates are that HIV infection both in the U.S. and abroad may be lower than those currently widely held.

We are attempting to build a model for analysis of the history of HIV spread through back calculations based on the number of AIDS cases and the natural history of HIV infection. This model should help to assess how generalizable the conclusions of small studies will be.

Trinidad and Jamaica

Because of our ongoing studies with the University of West Indies campuses in Trinidad and Jamaica, we have been asked to assist in the evaluation of HIV infection in these HTLV-I-endemic areas. Unlike HTLV-I, which appears to be a

long-standing and widespread virus in these area, HIV is newly introduced, with seropositivity and clinical AIDS confined so far to known risk group members. As in other low rate areas, the major risk factor for seropositivity appears to result from homosexual contact with persons from AIDS areas. An interesting finding from one study in Trinidad suggests the possibility that persons co-infected with HTLV-I and HIV may have an amplified risk for AIDS.

Related Retroviruses

We maintain an active program to isolate and characterize known retroviruses from different areas of the world in the hope that strain differences may provide a clue to the clinical variation in progression to AIDS or in "natural resistance," if such exists. We also seek to find new agents. Several lines of evidence suggest the concept that there may be several other retroviruses in some parts of the world. Their existence and relationship to other viruses needs to be demonstrated and their relationship to human disease described. Current areas of interest are in Greece and in New Guinea. In addition, we are seeking samples from persons infected many years ago to examine changes in retroviruses that have occurred over time. To do this with HTLV-I, we have arranged a collaboration with the Veterans Administration Hospital in Washington, D.C., to examine collections of sera obtained from drug abusers in the early 1970s. Such studies will also help to determine the health impact of infections, since subjects in this study can, in theory, continue to be followed through the V.A. system.

PROJECT 3: Lymphotrophic Herpes Viruses and Cancers

The well-documented relationship between EBV (Epstein-Barr virus) and both Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC) served as a model for studies of a newly discovered herpesvirus, HHV6, which was initially called HBLV because of its apparent predilection for B-lymphocytes, a tropism that is now known to extend to T-lymphocytes, megakaryocytes and other non-lymphoid cells. A potential relationship to human lymphoma was supported by serologic studies identifying elevated antibody titers in several human malignancies, including Hodgkin's disease and acute lymphocytic leukemia, and the detection of viral genome in three human B-cell lymphomas. Studies are now focusing on the evaluation of newly developed assays for HHV6 antibodies to test the suggested associations between this virus, which is widely spread in all population studies to date, and specific diseases. In a related effort, antibodies to antigens produced by another oncogenic herpesvirus, herpesvirus saimiri (a virus normally found in squirrel monkeys which produces lymphomas in owl monkeys and marmosets) was detected in several healthy animal handlers and controls, but the significance of these findings remains to be determined.

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CONTRACTS IN SUPPORT OF THIS PROJECT

MEDICAL RESEARCH COUNCIL (NO1-CP3-10150-00)

Title: Epidemiology Surveys for Human Retroviruses

Current Annual Level: $848,985

Person Years: 10

Objectives: To support international studies of human retroviruses and their relationship to illness.

Major Contributions: Studies are ongoing in Africa, Europe, South and Central America and the Caribbean.

KUAKINI MEDICAL CENTER (NO1-CP5-1023-00)

Title: HTLV-I in Migrant Populations in Hawaii and Okinawa

Current Annual Level: $193,450

Person Years: 2

Objectives: To determine the changes in HTLV-I in groups immigrating from a high prevalence area (Okinawa/Southern Japan) to a low prevalence area (Hawaii).

Major Contributions: Preliminary analysis indicates a steady decline of HTLV-I prevalence. The relationship to disease symptoms is still under study.

CARIBBEAN EPIDEMIOLOGY CENTER (NO1-CP6-1022-00)

Title: Epidemiology of Human T-cell Leukemia/Lymphoma Virus in Trinidad and the Caribbean Region

Current Annual Level: $268,694

Person Years: 4

Objectives: To support studies in Trinidad on the relationship between HIV and HTLV-I.

Major Contributions: HTLV-I is endemic in Trinidad, but HIV was introduced largely through the homosexual community.

BRATON BIOTECH (NO1-CP5-1086-00)

Title: Immunologic Studies of High Risk Groups

Current Annual Level: $568,125

Person Years: 5

Objectives: To provide immunologic tests (T-lymphocyte subsets) on cohorts under study for the effects of human retroviruses and related malignancies.

Major Contributions: Ongoing evaluation of the immunologic status of homosexual men and hemophiliac patients have documented a steady decline over the past six years.

RESEARCH TRIANGLE INSTITUTE (NO1-CP-61013)

Title: Support Services for Epidemiologic Studies of HTLV-III and Related Viruses

Current Annual Level: $277,000

Person Years: 17

Objectives: To support retrovirus-related studies with field workers and computer facilities.

Major Contributions: Project staff have contributed to studies of nearly every major effort undertaken by Viral Epidemiology staff.

UNIVERSITY OF GHANA (NO1-CP5-1009-00)

Title: Studies on the Epidemiology of Potentially Oncogenic and Immunosuppressive Viruses in West Africa

Current Annual Level: $45,000

Person Years: 4

Objectives: To examine the entrance of HIV and the prevalence of other human retrovirus and to determine their relationship to human disease.

Major Contributions: Data indicate HIV entered Ghana in 1986, largely through prostitutes returning home from neighboring countries. Levels of knowledge are good and may be contributing to behavior changes to prevent further spread.

BIOTECH RESEARCH LABORATORIES, INC (NO1-CP2-1007-00)

Title: Laboratory Support for Specimen Processing and Storage of Biological Specimens from Persons at High Risk of Cancer

Current Annual Level: $301,538

Person Years: 6

Objectives: To provide services for organizing, aliquoting, storing and shipping of specimens obtained by several sections of the Environmental Epidemiology Branch.

Major Contributions: This repository has received tens of thousands of samples annually and has processed them efficiently.

UNIVERSITY OF THE WEST INDIES (NO1-CP3-1006)

Title: Epidemiology of HTLV-I in Jamaica

Current Annual Level: $311,416

Person Years: 5

Objectives: To undertake in-depth surveys of HTLV-I in an endemic area.

Major Contributions: Studies of over 15,000 persons have provided a complete profile of the transmission and distribution of HTLV-I. Data about the health risks of HTLV-I infection are in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05526-02 EEB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Analytical Investigations of Selected Issues in Human Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. A. Brinton	Chief, Environmental Studies	EEB	NCI
Others:	K. P. Cantor	Epidemiologist	EEB	NCI
	G. Gridley	Statistician (Health)	EEB	NCI
	R. N. Hoover	Chief	EEB	NCI
	C. Schairer	Statistician (Health)	EEB	NCI
	M.H. Schiffman	Clinical Investigator	EEB	NCI

COOPERATING UNITS *(if any)*

28 BCDDPs;Hutzel Hosp (J Wolfe);GW Univ (L McGowan);5 Comp Can Ctrs;Gorgas Mem Lab (W Reeves);Georgetown Univ (R Kurman);NY Health Dept (P Nasca);IL Cancer Council (K Mallin);3 Kaiser Med Ctrs (A Glass, G Friedman, W Finkle);Mayo Clinic (J Melton);10 SEER Ctrs;Chin Acad Med Sci (J-Y Li).

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Environmental Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
8.0	6.0	2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to investigate, in analytic studies, the etiologies of selected cancers. Specific cancer sites and hypotheses are selected for which the need for investigation is clear but which have been difficult to study elsewhere. Studies focus either on tumors that have not been studied analytically before (e.g., because of the rarity of the tumor) or on hypotheses that are difficult to assess (e.g., because of the prevalence of the exposure or the need to detect an effect at low levels of exposure). A major emphasis within this project area has been on defining the etiology of female tumors. In many of these studies, as well as in selected others, attempts have been made to assess, exposures through interdisciplinary approaches. Studies completed within the last year have assessed the importance of parenchymal patterns to subsequent breast cancer risk, type-specific papillomaviruses to cervical abnormalities, a variety of risk factors for ovarian cancer in both high and low-risk areas, reproductive and contraceptive factors related to risk of trophoblastic diseases, and combination estrogen and progestin treatment as a risk factor for breast and endometrial cancers. Analyses have revealed an increased risk for bladder cancer associated with long-term residence in places served by chlorinated surface drinking water sources, and a suggestion of an increased risk of leukemia and non-Hodgkin's lymphoma associated with exposure to chlorinated hydrocarbon pesticides. A case-control study of childhood leukemia in China also demonstrated, for the first time, a link with chloramphenicol use.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

L. A. Brinton	Chief, ESS	EEB	NCI
K. E. Brock	IRTA Fellow	EEB	NCI
K. P. Cantor	Epidemiologist	EEB	NCI
G. Gridley	Statistician (Health)	EEB	NCI
P. Hartge	Epidemiologist	EEB	NCI
R. Herrero	Visting Fellow	EEB	NCI
A. Hildesheim	Epidemiologist	EEB	NCI
R. N. Hoover	Chief	EEB	NCI
C. J. Jones	Staff Fellow	EEB	NCI
C. Schairer	Statistician (Health)	EEB	NCI
M. H. Schiffman	Clinical Investigator	EEB	NCI
X. O. Shu	Visiting Fellow	EEB	NCI
R. G. Ziegler	Nutritional Epidemiologist	EEB	NCI

Objectives:

(1) To identify tumor sites for which there are a number of unusual demographic, laboratory or clinical associations indicating the necessity to evaluate a broad range of potential exposures. (2) To identify populations in which in-depth evaluations can be most efficiently carried out. (3) To design, conduct, and analyze these studies intensively.

Methods Employed:

Investigations of Female Tumors

1. A case-control study within the context of a multicenter breast cancer screening program, the Breast Cancer Detection Demonstration Project (BCDDP), involving over 10,000 interviews among women with either breast cancer, benign breast disease or no breast abnormalities, enabled a variety of newly emergent etiologic hypotheses to be evaluated.

2. In conjunction with the BCDDP case-control study, an investigation to evaluate the temporal effects of parenchymal patterns on risk of breast cancer was completed. This study focused on 266 women whose breast cancer was detected on the fifth annual screening examination, and on matched controls. Mammograms from the first, fourth, and fifth screening examinations were read blindly by Dr. John Wolfe (originator of the parenchymal pattern classification system), allowing the concordance of patterns between examinations, as well as the predictability of patterns for subsequent breast cancer, to be assessed in relation to information on standard breast cancer risk factors.

3. A follow-up study of over 60,000 participants in the BCDDP is being continued. Included for study are all women with breast cancer or benign breast disease detected during screening, as well as a sample of normal

volunteers. The addition of dietary and anthropometric data to the questionnaire will allow these factors, as well as others, to be prospectively assessed in relation to a number of outcomes.

4. A case-control study of endometrial cancer (described in detail in Z01CP05128-09 EEB) is underway in five different study areas. Although a major emphasis is on nutritional exposures, the study also provides the opportunity to evaluate several emergent hypotheses for this tumor, including the roles of added progestin therapy, alcohol, smoking and endogenous hormones.

5. Ovarian cancer patients (350) diagnosed between 1978 and 1981 in 25 Washington, D.C. area hospitals and women hospitalized for other conditions (350) were interviewed in their homes to collect information about medical, family, reproductive and menstrual histories, use of exogenous estrogens, contraception, occupation, and smoking.

6. Data from a case-control study of 229 women with newly diagnosed ovarian cancer and an equal number of population-based controls, conducted in Shanghai, China during 1984-1986, were analyzed to determine whether risk factors in a low-risk area resemble those identified elsewhere.

7. A case-control study of invasive and in situ cervical cancer has been conducted in conjunction with five Comprehensive Cancer Centers. Home interviews were obtained from 481 patients with invasive disease, 293 with in situ cancer, and 801 random digit dialing controls. Interviews focused on reproductive and menstrual history, sexual behavior, medical events, contraceptive usage, smoking and alcohol use, diet, and family history of cancer.

8. A case-control study of 117 cases with in situ cervical cancer and 196 community controls was conducted in Sydney, Australia. Interviews focused on sexual, reproductive and medical history, as well as dietary intake, described in detail in Z01CP05128-09 EEB.

9. To determine the reasons for high rates of invasive cervical cancer, a case-control study was conducted in four Latin American countries--Colombia, Costa Rica, Mexico, and Panama. The study included personal interviews with approximately 750 women with invasive cervical cancer and 1,500 matched controls. The husbands of sexually monogamous female subjects (approximately 200 case and 500 control husbands) were interviewed in conjunction with a clinical examination oriented toward assessing genital hygiene, circumcision status and evidence of infection. Blood samples and cervical or penile scrapings were obtained from all subjects to provide further information on the role of infection agents.

10. A study was conducted in three hospitals in Washington, D.C. to assess how biochemical measures of smoking exposure and viral DNA presence interact in determining a woman's risk of cervical intraepithelial neoplasia. A total of 3188 women were included.

11. A study to define methods for detecting papillomavirus-related DNA sequences in the cervix was conducted at Montefiore Medical Center in New York City. Patients (150) in a colposcopy clinic were sampled using an exocervical swab plus endocervical swab, versus a cervicovaginal lavage.

12. An interlaboratory study of human papillomaviral (HPV) detection in clinical specimens using Southern blot assays was conducted with four laboratory collaborators. Forty masked identical DNA samples were distributed and the typing results were compared.

13. A prospective study of early HPV infection in cytologically normal women has been initiated. A key unresolved question is the significance of HPV infection in apparently normal women. A cohort of 25,000 Pap smear screenees will be included. Cervicovaginal lavages will be frozen to permit a subsequent nested case-control study of incident atypia and dysplasia in relation to pre-morbid HPV type-specific infection. Follow-up is scheduled to last three years.

14. A case-control study to determine environmental exposures which increase the risk of vulvar and vaginal cancers is nearing completion. Approximately 250 vulvar cancer and 75 vaginal cancer cases are expected to be ascertained over a 30-month period in Chicago and upper New York State. Subjects are being interviewed and 30 ml of venous blood drawn to obtain serologic levels of micronutrients and infectious agents. In addition, fresh tumor specimens have been obtained for a subset of the cases (150 women) in order to determine human papillomavirus types associated with these tumors.

15. A case-control study of hydatidiform mole, invasive mole and choriocarcinoma in Beijing, China was completed. This study included interviews with 189 patients with complete hydatidiform mole, 142 with invasive mole, 30 with choriocarcinoma and 722 population controls. Personal interviews enabled evaluation of a variety of risk factors for these poorly understood conditions.

16. Data were analyzed from a case-cohort study conducted in Sweden of 23,000 women who had all been prescribed non-contraceptive estrogens. All of the cases and a random sample of the cohort were administered questionnaires which elicited detailed information on estrogen exposure and selected risk factors. Based on the distribution of estrogen use in the sample, observed to expected ratios for various cancer sites in the total cohort were calculated. The case-cohort analysis was supplemented with a case-control analysis, which permitted control of confounding factors.

17. A follow-up study of 2,335 women evaluated for infertility at the Mayo Clinic during the period 1935-1964 was analyzed. Information on reasons for infertility (hormonal vs. other) was evaluated in relation to subsequent cancer morbidity.

18. A number of research projects have been undertaken in collaboration with three prepaid health plans. These include 1) an evaluation of changes in breast cancer risk over time in one health plan; 2) a case-control analysis of 458 breast cancer cases and an equal number of controls to evaluate the relationship to risk of diazepam use; 3) a record-abstract, case-control study of 489 cases of histologically confirmed epithelial ovarian cancer and 604 matched controls from two plans, designed to determine the relationship of several medical conditions and procedures and therapeutic drug use to risk of this malignancy; 4) a case-control study of 124 breast cancer cases of 2615 women with benign breast disease, where available pathology slides will enable evaluation on subsequent cancer risk of the interaction of hormone use and a dysplasia index; and 5) a nested case-control study of HPV infection in relation to progression of cervical intraepithelial neoplasia, using stored cytologic specimens and in situ DNA-DNA hybridization methods for HPV types 16, 18, and 31.

Other Investigations

19. All bladder cancer patients (4,000) who were diagnosed in 1978 in five states and five metropolitan areas were identified, and controls (7,000) were drawn from the general population of the 10 geographic areas. Subjects were interviewed in their homes to collect data about saccharin use, smoking habits, occupational history, residential history, sources of drinking water, fluid intake, hair dye use, coffee-drinking, and medical history. Histological data were collected from pathology reports. This major study is nearly complete (see previous Annual Reports for publications). One area of continuing interest is the apparent excess number of bladder cancer cases in males compared to females, independent of smoking and occupation.

20. A large study of tumors that occur excessively among blacks is underway with the following objectives: (1) to identify race-specific risk factors for four cancer types--pancreatic, esophageal, prostatic and multiple myeloma; (2) to estimate the extent to which the risk factors may explain the black/white difference in incidence rates; and (3) to use laboratory data to relate risk to certain biochemical indicators (e.g., hormones and trace metals), to evaluate the role of genetics in the development of multiple myeloma, and to examine differences in baseline levels of micronutrients between blacks and whites. The study design involves blacks and whites who are newly diagnosed over the time period 1986-1989 in hospitals located in New Jersey, Atlanta, and Detroit. Controls are being selected from the population of each of these three areas. All subjects are being administered a standardized questionnaire. In addition, blood is being drawn on a sample of prostate cancer cases and controls and on all male multiple myeloma cases.

21. A case-control study of leukemia and non-Hodgkin's lymphoma was conducted in Iowa and Minnesota. Interviews were conducted with 600 leukemia patients, 600 lymphoma patients, and 1,200 population-based controls. Information collected included occupational and medical history, farm-related exposures, exposure to ionizing radiation, solvents and pesticides, smoking, socio-economic status, and family history of cancer. Data analysis is in progress.

22. A population based case-control study of 309 childhood leukemia cases and 619 control children was conducted in the Shanghai urban area to explore risk factors and to examine etiologic variation by different histopathologic cell types.

23. A case-control study of penile cancer in Hunan Province, China has been initiated. Included will be 100 patients with penile cancer, an equal number of population controls, and the wives of both groups. Interviews as well as blood specimens and penile or cervical material are being obtained to evaluate a variety of etiologic hypotheses, including the role of papillomaviruses.

24. The computer-based file of Veterans Administration hospitalization records has been expanded to 4.4 million veterans discharged between July 1, 1969 and September 30, 1985. Disease cohorts have been correspondingly increased in size, giving more stable estimates of cancer risk (Standardized Incidence Ratios (SIRs)). Internal rates were re-computed, and external rates are in the process of re-computation for these comparisons. Initial cohorts of interest include patients with rheumatoid arthritis (50,660 veterans), pernicious anemia (7,524), lupus erythematosus (2,687), Sjogren/sicca syndrome (1,857), scleroderma (2,455), acromegaly (1,212), multiple sclerosis (16,699), cholelithiasis (89,364), and cholecystectomy (75,607). In addition, a nested case-control medical abstract study of rheumatoid arthritis and hematopoietic cancers is being planned.

25. A large excess of non-Hodgkin's lymphoma has been documented in renal transplant patients and may be related to immunosuppressive therapy, persistent antigenic challenge from the graft, or both. To determine whether immunosuppression resulting from chronic renal failure is associated with an elevated risk of certain tumors such as non-Hodgkin's lymphoma, we studied cancer incidence in a national cohort of 28,049 patients in the United States with chronic renal failure who received maintenance dialysis for at least six months (totaling 66,706 person-years of observation).

Major Findings:

Female Tumor Studies

Analyses of information from the BCDDP study showed that age at menarche was significantly inversely related to breast cancer risk. A bilateral oophorectomy was associated with a lowered risk relative to natural menopause at a comparable age, which may reflect the more precipitous decline in endogenous hormones associated with surgery. Analysis from the control population of the study indicated that parity, irregularity of menstrual cycles before age 25 or first livebirth, and high socioeconomic status were significantly positively related to menopausal age. The risk of breast cancer among women with P2 or DY parenchymal patterns as compared with N1 patterns was 2.7, an association comparable in strength but independent of other risk factors in this population.

In the case-control study of ovarian cancer in the Washington, D.C. area, menopause induced by hysterectomy, with preservation of both ovaries, was related to decreased risk. Infertility was associated with increased risk, apart from the effect of nulliparity. Parity was confirmed to be the most important protective factor, except in the serous subtype, suggesting that the histologic types should be considered separately. Tumors of low malignant potential shared the epidemiologic risk factor profile of invasive cancers.

The case-control study of ovarian cancer in Shanghai showed that, similar to high-risk areas, nulliparity increased risk (odds ratio, OR=1.9) and number of births was inversely associated. Early menarche and late menopause were associated with increased risks, as was a history of ovarian cysts. Although oral contraceptive use did not decrease risk, tubosterilization and IUD use were associated with 40-50% reductions in risk.

Analysis of data from the U.S. cervical cancer study showed that multiple sexual partners and early age at first sexual intercourse were important risk factors. Those with multiple births were at significantly elevated risks, even after adjustment for sexual practices. Histories of specific infections involving the genital tract were poor predictors of risk, but those with non-specific diseases were at elevated risk.

Analysis of data from the case-control study of in situ cervical cancer in Australia found that women with more than 7 sexual partners had a sevenfold risk compared to those with 0-1 partner. Risk also increased with duration of oral contraceptive use (OR=2.0 for more than 6 years of use), and with amount and duration smoked.

Results from the pilot phase of the Latin American cervical cancer study showed that more cases than controls had evidence of prior infection with papillomavirus types 16 or 18 as measured by filter in situ DNA hybridization techniques. The rate of positivity among the control population was, however, higher than anticipated, resulting in an OR of 2.7, an association of lesser magnitude than hypothesized on the basis of laboratory findings.

Preliminary results from the Latin American cervical cancer study indicated an effect on risk among females of number of sexual partners, age at first intercourse, and interval since last pap smear. Surprisingly, an effect of multiple pregnancies persisted after adjustment for sexual and other variables, with risks rising to over fourfold for those with 10 or more pregnancies. A relationship to cervical cancer risk of sexual behavior of the husbands was also apparent, although to a lesser extent than previously hypothesized.

Preliminary results from the study of cervical dysplasia, smoking, and papillomavirus infection suggested that the risk of apparent dysplasia may be increased up to eightfold in HPV-infected women who smoke compared to noninfected nonsmokers. Infected nonsmokers had a risk of about 3, while noninfected smokers had a risk of about 2.

Methods studies for detecting cigarette smoke constituents and metabolites in cervical mucus showed that the flush was the best collection technique, providing more sample than scrape or swab. Mutagenicity assays were found not to be useful in assaying cervical mucus. Instead, nicotine and cotinine assays appeared very promising.

The interlaboratory study of HPV detection by Southern blot revealed considerable variation in typing when this "gold standard" assay was used, enough to explain some of the discrepant findings in previously published research.

A comparison of risk factors for hydatidiform mole and invasive mole showed that a history of a prior full-term birth was associated with reduced risk for both conditions, while previous miscarriage or abortions increased the risk of invasive mole but not complete mole. A history of infertility was associated with reduced risk, but those who reported use of herbal medicine during a previous pregnancy were at excess risk. Use of oral contraceptives was positively associated with risk of complete mole, but no relationship was observed for invasive mole.

In the case-cohort study of breast and endometrial cancers conducted within the prospective study in Sweden, positive trends with increasing total duration of estrogen treatment were found for both cancers. A protective effect of addition of cyclic progestins to treatment was not found for breast cancer, whereas for endometrial cancer no significant risk was found for estrogen usage that had been opposed by progestins. An additional case-control analysis evaluated the effects of several risk factors for breast and endometrial cancer in the cohort of women compared to the background population.

In the infertility follow-up study, most cancers occurred at expected frequencies, with the exception of cancers of the thyroid and other endocrine glands. Patients with progesterone deficiencies had a 20% overall higher risk than those with other causes of infertility, with excesses deriving primarily from cancers of the lung, cervix, endometrium, ovary, thyroid, and for melanoma. Breast cancer risk, however, was not elevated in all patients or those with progesterone deficiencies, failing to support previous suggestions that this is a high-risk group.

Analyses within the prepaid health plans have shown that the age-adjusted rate of breast cancer has risen from 69.2 in the early 1960s to 100.3 per 100,000 in the early 1980s. Adjusted for age and stage, the rates for estrogen receptor-positive tumors have more than doubled, while the rates for estrogen-negative tumors have risen only slightly, with the bulk of these increases presumably not due to any increase in use of mammographic screening. In the breast cancer case-control analysis, diazepam use was found to be associated with a risk of 0.7. There was, however, no consistent evidence of a dose or duration-response relationship. The analysis of data from the ovarian cancer study found that ovarian cyst was a major predictor of risk for early onset disease (<50 years), while uterine bleeding or progestin use were important risk factors for older subjects.

Other Investigations

The National Bladder Cancer Study provided the opportunity to show that risk profiles for two uncommon histologic types of bladder cancer, squamous cell and adenocarcinoma, differ from each other and from the common transitional cell carcinoma of the bladder. Risks of transitional cell carcinoma of the bladder in the United States among whites are approximately twice those among blacks. Although some of the differences in risk was due to confounding by cigarette smoking and occupation, whites remained at 60% increased risk compared to blacks after adjustment. The remaining difference in risk may be due, in part, to diagnostic differences.

Analyses of National Bladder Cancer Study data also revealed a modest but highly significant association of risk with tap water intake, but not other beverages. The risk gradient with intake was most pronounced among subjects with at least 40 years of residence at places served by chlorinated surface drinking water sources and was not apparent among long-term ground water users. An overall effect of duration of exposure to chlorinated surface drinking water was found in women and nonsmokers of both sexes.

Preliminary analysis of data from the leukemia and non-Hodgkin's lymphoma (NHL) study in Iowa and Minnesota suggested a relationship with use of some chlorinated hydrocarbon pesticides at least 20 years prior to diagnosis. There was no association of all leukemia or NHL with farming occupation. Suggestive associations were observed for both diseases with hair dye use, although the numbers of users was small.

The case-control study of childhood leukemia in Shanghai confirmed previous observations of an association of risk with intrauterine x-ray exposure. In addition, a significant dose-response relation was seen with use of certain antibiotics, including chloramphenicol. Other risk factors suggested were heavy birth weight, late birth order, and maternal exposure to chemicals during pregnancy.

In the first analysis completed using Veterans Administration hospitalization records, the expanded cohort of 5,161 while males with pernicious anemia was found to have significant excesses for all cancers (SIR=1.2) and cancers of the buccal cavity and pharynx (SIR=1.8), stomach (SIR=3.2), and for melanoma (SIR=2.1), multiple myeloma (2.1), myeloid leukemia (SIR=3.7) and other or unspecified leukemia (SIR=4.0).

Compared with national incidence rates, dialysis patients demonstrated a relative risk for cancer of 0.9. Moderate excesses of leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, thyroid cancer and biliary tract cancer were found, but were not statistically significant. Patients with chronic glomerulonephritis had the highest risk of non-Hodgkin's lymphoma (RR=2.6).

Publications:

Bergkvist L, Adami HO, Persson I, Schairer C. Risk factors for breast and endometrial cancer in a cohort of women treated with menopausal estrogens. Int J Epidemiol (In Press)

Blair A, Cantor KP, Gibson R, Everett G, Schuman L, Burmeister L, Van Lier S, Blattner W. Lymphatic and hematopoietic cancer among farmers. In: Dosman J., eds. Proceedings of the International Symposium on Health and Safety in Agriculture. Boca Raton: CRC Press (In Press)

Blair A, Cantor KP, Zahm S, Burmeister L, Van Lier S, Gibson R, Schuman L. Cancer and pesticides among farmers. In: Schroeder L, ed. Pesticides and ground water: a health concern for the midwest. Navarre, MN: Freshwater Foundation, 1988;169-97.

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Brinton LA, Hamman RF, Huggins GR, Lehman HF, Levine RS, Mallin K, Fraumeni JF Jr. Sexual and reproductive risk factors for invasive squamous cell cervical cancer. JNCI 1987;79:23-30.

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Cantor KP, Blair A, Everett G, Van Lier S, Burmeister L, Dick FR, Gibson RW, Schuman L. Hair dye use and risk of leukemia and lymphoma. Am J Public Health (In Press)

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Carter CL, Schatzkin A, Jones DY, Brinton LA. A prospective study of familial, socioeconomic and reproductive risk factors for breast cancer in a cohort of U.S. women. Public Health Rep (In Press)

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CONTRACT IN SUPPORT OF THIS PROJECT

WESTAT, INC. (NO1-CP6-1078)

Title: Continuation of Follow-up on Participants in the Breast Cancer Detection Demonstration Project

Current Annual Level: $314,402

Person Years: 1.5

Objectives: The main objectives of this project are to evaluate through a prospective study design such risk factors for breast cancer incidence as exogenous menopausal estrogen use, smoking, alcohol consumption, and diet; to determine etiologic factors for other cancers, such as lung, endometrial, ovarian and colorectal cancers; and to examine the effects of exogenous estrogens on mortality from heart disease, and hospitalization for fractures, gallbladder disease and diabetes.

Methods: This contract is funding a continuation of a cohort study initiated in 1981 on a sample of approximately 61,000 women who had previously participated in the Breast Cancer Detection Demonstration Project (BCDDP), a breast cancer screening program co-sponsored by the National Cancer Institute and the American Cancer Society. Self-administered mail interviews are being collected biannually, yielding two interviews per subject during the five years of the study. Death certificates are being collected for all deceased subjects, and all newly diagnosed cancers are being validated through collection of operative and pathology reports.

Major Contributions: To date, eight waves of questionnaires have been mailed to approximately 20,000 participants. The earliest wave of questionnaires has yielded over a 70% response rate. Over 300 subjects are known to be deceased, and death certificates have been requested. Validation procedures are underway to obtain verification of all reported cancers, and the first mailout resulted in a 93% return rate from doctors or hospitals. All information is being keypunched, and computer files generated to allow eventual analyses of these prospectively collected data.

ANNUAL REPORT OF

THE RADIATION EPIDEMIOLOGY BRANCH
EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1987 through September 30, 1988

This is the fifth annual report of the Radiation Epidemiology Branch, which was created in February 1984. The objectives of the Branch are to identify and quantify the risk of cancer in populations exposed to ionizing radiation, alone or in combination with cytotoxic drugs, and to explore and formulate models of radiation carcinogenesis that may help define basic mechanisms of cancer induction, including the integration of experimental findings with epidemiologic observations. In August 1987, Dr. Dale Preston was appointed an Expert statistician with the Branch. During the past four years, he was Chief of the Computer Center at the Radiation Effects Research Foundation (RERF) in Hiroshima, Japan. In November, Seymour Jablon was appointed an Expert statistician. Mr. Jablon was the former Director of the Medical Follow-up Agency at the National Academy of Sciences - National Research Council. Also in November, Dr. Charles Mays was appointed an Expert radiobiologist. He was a Professor of Physics and Pharmacology at the University of Utah during the past 30 years. In December, Peter Inskip was appointed under a P-authority. He is a doctoral student in epidemiology at the Harvard School of Public Health. In January, Dr. Zhang Shouzhi was appointed a Visiting Associate. For the past four years he has participated in the Low-Level Natural Background Radiation Study being conducted by the Laboratory of Industrial Hygiene, Beijing, China. Guest researchers during this past year included Dr. Tao Zufan from the Laboratory of Industrial Hygiene, Beijing, China; Dr. Zha Yongru from the Guangdong Radiation Protection Society, Guangzhou, China; Dr. Jorge Olsen from the Danish Cancer Registry, Copenhagen, Denmark; Dr. Faith Davis from the University of Illinois School of Public Health; and Dr. Suminori Akiba from RERF in Hiroshima, Japan. The Branch also attracts visiting scientists from a number of countries for relatively short periods of intense collaboration. This past year, visiting scientists have come from England, Finland, Norway, France, Belgium, Canada, Germany, Japan, Sweden, Denmark, Israel, the Netherlands, and the People's Republic of China. One staff member departed during the past year: Dr. Maria Blettner, Expert biostatistician, accepted a position at the University of Liverpool, England.

RESEARCH PROGRAM:

Studies of populations exposed to ionizing radiation are being conducted to strengthen the quantitative basis for risk estimation, especially at low doses, to improve understanding of the role of host and environmental factors on radiogenic cancer risk, and to provide insights into carcinogenic mechanisms. Better data are needed on which to base regulatory and other decisions about the

potential hazard from medical, occupational, and environmental exposures, and to assess the value of exposure avoidance as a means of cancer prevention.

Medical Exposure Studies: Studies of populations exposed to medical irradiation have great potential for quantifying late radiation effects because (1) exposures can usually be accurately estimated, (2) nonexposed patients are often available for comparison, (3) useful information on other risk factors can frequently be obtained from existing records, and (4) medical facilities often follow patients for long periods of time after treatment. The only evidence that a cancer can be induced by ionizing radiation for relatively insensitive tissues comes from patient populations given high-dose, partial body, therapeutic irradiation. For other sites, the best evidence on low-dose risk comes from populations given multiple, low-dose, diagnostic irradiation resulting in high cumulative exposures.

An international study of cervical cancer patients, including over 200,000 women treated by radiation or surgery, is nearing completion. For the first time, radiation regimens used to treat cervical cancer patients were found to be associated with a small, but significant, increased risk of leukemia. Risk was found to increase with increasing radiation dose and then decrease at the highest doses. This pattern is consistent with experimental data for which the down-turn in risk at high doses has been interpreted as due to killing of potentially leukemic cells. These data provide convincing evidence that cellular killing may significantly influence the carcinogenic response to radiation in humans. The excess relative risk of 0.9% per rad was consistent, though slightly lower, with that computed from other series of radiogenic leukemia. New cancers linked to radiation included cancers of the rectum and vagina. Very high doses, on the order of several thousand rad, were also found to increase the risk of cancers of the bladder and possibly uterine corpus, bone, cecum, and non-Hodgkin's lymphoma. For all female genital cancers taken together, a sharp dose response was observed. Doses on the order of several hundred rad increased the risk of stomach cancer, and possibly kidney cancer, but not pancreatic cancer. Doses greater than 600 rad to the ovaries resulted in a 23% reduction in breast cancer risk. A biochemical study of some 300 women with cervical cancer suggested that adrenal damage by radiation may have lowered estrogen and androgen levels and contributed to a low breast cancer risk, which was evident even among postmenopausal women. Although no overall risk was found for direct exposure to the breast, despite an average dose of 31 rad, there was a suggestion of a dose response among women whose ovaries had been surgically removed. Radiation also was not found to increase the risk of cancers of the small intestine, colon, and vulva, and Hodgkin's disease, multiple myeloma, and chronic lymphocytic leukemia. A twofold risk of radiogenic thyroid cancer, however, was suggested following an average dose of 11 rad.

Several studies of childhood irradiation are being conducted. The minimal confounding effect of other carcinogenic influences, such as smoking or occupation, and the possible greater susceptibility of young people to environmental carcinogens, enhances the chance of detecting increased risks due to therapy. A study of 3,000 children treated for lymphoid hyperplasia with radiation or surgery in Boston was completed. Physical examinations had been performed on more than 1,000 patients to determine more accurately the risk of thyroid nodules and to account for the potential detection bias in previous studies where only radiation-exposed persons were screened. An excess of both thyroid cancer and nodules in the exposed population was identified following a mean

dose of 24 rad. However, the radiation risk was much lower than that estimated from a mail survey of the same population, suggesting that questionnaire studies of thyroid cancer might be biased due to extreme underascertainment of thyroid diseases in the non-exposed populations. A further follow-up of 10,000 children irradiated for ringworm of the scalp in Israel, and 15,000 matched comparison persons, revealed an excess of thyroid cancer and thyroid nodules following doses on the order of nine rad. An elevated risk of brain tumors, skin cancer and leukemia has also been linked to scalp radiotherapy. A biochemical epidemiologic study has continued to evaluate whether the risk of radiogenic thyroid cancer (and skin cancer) might be related to increased host susceptibility associated with heterozygosity for ataxia telangiectasia. Ataxia telangiectasia is a genetic disorder relatively common among North Africans; and North African immigrants were found to be at highest relative risk for radiogenic thyroid disease in this study.

Over 9,000 persons who survived at least two years after a diagnosis of childhood cancer in 13 hospitals in the U.S. and other countries have been studied for the risk of second cancer development. Detailed medical records have been abstracted on cases and controls to quantify the risks associated with radiation or chemotherapy treatments. Detailed dosimetry has been performed to estimate radiation doses to individual organs or tissues. Among second malignancies, bone cancer was associated with high-dose radiation therapy as evidenced by a strong dose-response relationship. Patients treated for retinoblastoma, a heritable disease associated with a propensity for developing subsequent osteosarcomas, were not at unusually high relative risk for radiogenic bone cancer when compared to children treated for other malignancies. A 50-fold increased risk of thyroid cancer was related to radiotherapy. Exposures as high as 6,000 rad were associated with a high risk and there was no evidence of a downturn in risk. Contrary to previous reports, actinomycin-D was not found to protect against the development of radiation-induced cancers of the bone or thyroid.

A population-based case-control study of thyroid cancer in Connecticut was published. Home interviews were conducted on 159 persons who developed thyroid cancer between 1978 and 1980, and on 285 controls. A high risk of thyroid cancer was associated with radiotherapy for benign head and neck diseases when exposure occurred under age 10. Few persons born after 1945 reported prior radiotherapy, a finding consistent with the declining use of radiation to treat benign conditions in the 1950s. Consumption of vegetable goitrogens appeared to decrease risk. Among women who received radiotherapy, subsequent live births appeared to enhance risk. Approximately 9% of all thyroid cancers could be attributed to prior childhood head and neck irradiation. Other factors showing positive associations with thyroid cancer included a previous history of thyroid nodules, goiter or benign breast disease. Among women who developed thyroid cancer prior to age 35, multiparity and miscarriage were also risk factors.

The risk of cancer following multiple chest fluoroscopies during pneumothorax treatment of tuberculosis between 1930-1954 was further evaluated in Massachusetts, Connecticut, and Denmark. The study of over 13,385 persons discharged alive from Massachusetts sanatoria indicated that repeated, relatively low radiation doses pose some future risk of breast cancer, the risk appears cumulative, adolescence is an especially sensitive age, and women over 40 years of age at exposure are at little or no risk. A modest increased risk

of cancer of the esophagus was suggested. In contrast, no excess risk of lung cancer was found, despite average cumulative doses of 84 rad, and no consistent dose response was seen for leukemia or multiple myeloma. Results from a study of 163 women, which included physical examination of the head and neck and blood studies, suggested that thyroid nodular disease might result from multiple low-dose exposures and that irradiation may have predisposed to autoimmune thyroid disease.

A study was conducted of 1,030 women with scoliosis seen at four Minneapolis-area hospitals between 1935 and 1965. These women received large numbers of spinal x-ray examinations during adolescence to monitor spinal curvature. The risk of breast cancer was found to increase with increasing number of x-rays and with increasing radiation dose to the breast (mean = 12 rad). These data suggest that frequent exposure to low-level diagnostic radiation during childhood or adolescence may increase the risk of breast cancer.

To evaluate whether diagnostic x-rays increase the risk of adult leukemia and lymphoma, a case-control study was conducted within two Kaiser prepaid health plans. Patients with leukemia (n=632), non-Hodgkin's lymphoma (NHL; n=324), and multiple myeloma (n=243) were matched to controls (n=1,431). Over 30,000 x-ray procedures were abstracted from hospital records and categorized, eliminating the possibility of response bias associated with interview studies. No association was found for chronic lymphocytic leukemia (RR=0.9; n=247), one of the few malignancies never linked to radiation. For all other forms of leukemia combined (n=385) there was a significant increase in risk with increasing number of x-rays; however, this trend progressively diminished when x-rays near the time of diagnosis were excluded. Patients with NHL were x-rayed more often than controls (RR=1.60); but the RR fell to 1.1 when x-rays within 2 years of diagnosis were ignored. These data suggest that x-rays might not be causal factors but simply related to conditions that portend the development of leukemia or NHL. For multiple myeloma, there were suggestive increases in risk that were not diminished by excluding x-rays in the intervals before diagnosis.

A significant risk of developing a second breast cancer was found among 27,000 breast cancer patients in Connecticut. Case-control studies of long-term survivors are being conducted in Connecticut and Denmark to learn whether the increased risk might be related to radiation therapy, especially among women treated after age 40. Preliminary data from Connecticut indicate an increasing risk of breast cancer with increasing dose to contralateral breast; however, risk was not elevated among long-term survivors. No risk of leukemia was linked to radiotherapy for breast cancer, providing further evidence that cell death predominates over cell transformation when high radiation doses are delivered to limited volumes of tissue. Women irradiated for Hodgkin's disease at a young age were found to be at high risk for developing breast cancer.

The incidence of thyroid cancer was evaluated in 35,074 patients examined for suspected thyroid disorders between 1951-1969 in Sweden with an average of 1.92 MBq (50 rad) of 131-iodine. Record-linkage with the Swedish Cancer Registry identified 50 thyroid cancers occurring 5 or more years after initial iodine-131 examination, in contrast to 39.4 expected (RR=1.27). Patients anticipated to be at highest risk, i.e., women (RR=1.1) and those observed for 10 or more years (RR=0.9), showed no evidence of a dose response. Overall, these data provide little proof that iodine-131 is carcinogenic in man and support the notion that

the carcinogenic potential of internal iodine-131 beta particles might be at least four times lower than that of external x-rays or gamma rays.

The time course and dose dependence of the incidence of bone sarcomas among 900 German patients treated with high doses of 224-radium have been analyzed in more detail. The distribution of excess bone sarcomas over time appears very similar to that seen for leukemia among the atomic bomb survivors, i.e., risk appears within 2 to 4 years after exposure and decreases to near normal levels after about 25 years. For a total dose of 224-radium, the effectiveness of inducing bone sarcomas appears to increase when the exposure is spread over time. For the first time, evidence of an excess of breast cancer has appeared.

A variety of analytic studies are underway. A population-based case-control study is being conducted among women treated for cancer of the uterine corpus to evaluate the dose-response relationship between radiation dose and risk of leukemia. A study of the carcinogenic effects of radiation therapy for gastric ulcer has continued. There is considerable controversy over the effectiveness of radioactive iodine in inducing malignancies, and ongoing studies include a second follow-up of 36,000 patients treated with radioactive iodine or surgery for thyrotoxicosis in the United States and a collaborative study of approximately 18,000 persons who received therapeutic doses of radioactive iodine in Sweden. A feasibility study in Israel showed that it will be possible to evaluate 30,000 persons given diagnostic iodine-131 for subsequent risk of thyroid cancer. Women are being studied who received radiation therapy for benign gynecological disorders in Massachusetts, New York, Rhode Island, Connecticut, and Sweden. Studies of over 2,000 women treated for infertility in New York and Israel have continued. A feasibility study of children receiving multiple chest fluoroscopies during heart catheterization was successfully completed at hospitals in the United States, England, and Israel; investigations in the Netherlands were initiated. An approach for studying patients receiving neutron therapy for cancer was developed. An essential part of the program of epidemiologic studies of medically irradiated populations is accurate dosimetry for specific organs. A team of medical physicists at the M. D. Anderson Hospital continued to work with the Branch on dosimetry problems. In addition, computer simulation codes, developed in collaboration with the Oak Ridge National Laboratory and the Center for Devices and Radiological Health, Food and Drug Administration have been used effectively to estimate radiation doses.

Atomic Bomb Survivor Studies: The life-span study (LSS) sample of 94,000 A-bomb survivors, plus 26,000 nonexposed residents, is perhaps the single most valuable source of epidemiological information on radiation carcinogenesis in humans. The Radiation Effects Research Foundation (RERF) has sole access to the LSS sample and has on file individual radiation dose estimates and current addresses for nearly all sample members. A virtually complete mortality follow-up is maintained. A clinical subsample, which includes most of the heavily exposed survivors, has been offered biennial medical examinations since 1958; about 12,000 have participated on a regular basis. An autopsy program, which now depends mainly on support from major city hospitals, has resulted in the accumulation of an extensive collection of tissue specimens. A dosimetry system, providing individual radiation dose estimates, has recently undergone a major revision. RERF plays the major role in the tumor, tissue, and leukemia registries in the two cities which supply the bulk of the diagnostic information for incidence and case-control studies. The Branch seeks to foster a close, long-term, scientific relationship with the RERF through a program of

collaborative studies supported by a multi-year research contract with the U.S. National Academy of Sciences, in effect since 1979.

A survey of breast cancer revealed a dose-related excess among women who were under age 10 at the time of the bombings (ATB), comparable to that seen among those who were teenagers ATB, while there was no evidence of excess risk among those exposed after age 40. The excess risk did not appear until ages at which breast cancer risk normally becomes appreciable. Excess risk was roughly proportional to dose; the additional number of cases provided direct evidence of an excess risk at breast tissue doses in the 8-16 rad range. A preliminary analysis of data from a current survey of colorectal cancer incidence has found a dose response for colon cancer, but no increased rectal cancer risk.

A recent case-control study of lung cancer indicated an enhanced lung cancer risk among nonsmoking wives of male smokers. Review of pathology materials from A-bomb survivors and Colorado uranium miners, carried out in May 1986 and May 1987 and currently being analyzed at NCI, may clarify the apparent epidemiological differences between these two populations in terms of lung cancer risk in relation to radiation dose and smoking. Preliminary findings from a case-control interview study of breast cancer indicates that age at first delivery, number of children, and length of lactation history are related to breast cancer risk among Japanese women and that they interact multiplicatively (synergistically) with radiation dose, while an additive relationship can be rejected. It appears that the female breast is more sensitive to radiation carcinogenesis when exposure occurs before the first pregnancy than afterwards, even when age at exposure and age at first delivery are accounted for. Preliminary findings from a study of colorectal cancer indicate a lower risk of colon cancer among subjects whose normal occupation involved significant physical exercise. Hormonal and micronutrient assays of stored serum samples for cancer cases and matched controls are being carried out at RERF and at collaborating laboratories in Japan. Because the samples were taken many years before the diagnosis of cancer, and because adequate numbers of cases and controls with stored serum are available, this study has especially good prospects of resolving issues raised by other similar studies of different populations.

A major initiative, taken in collaboration with the RERF histopathology laboratory, the tumor and tissue registries, and the Department of Epidemiology, is to enlist the cooperation of local pathologists to conduct a new series of site-specific cancer incidence studies. The new studies will rely on local sources of information and also will actively seek out information from national and regional registries from areas other than Hiroshima and Nagasaki. The first sites to be investigated are the female breast, uterine corpus, colon, rectum, bladder and kidney.

The effect of the new dosimetry changes on risk estimates has been evaluated. In terms of total kerma (essentially whole-body gamma plus neutron exposure), the risk estimates are 75% to 85% higher with the new dosimetry. At an assumed constant relative biological effectiveness of 10 for neutrons, the effect of the dosimetry revisions is to increase organ dose risk estimates, relative to those based on the old dosimetry, by 40% for nonleukemia and 80% for leukemia. There is substantial question of the linearity of the dose-response relationships in that a leveling off at high doses is seen for several sites.

Occupational and Environmental Exposure Studies: Although the possibility of increased cancer risk associated with chronic occupational exposure to x-ray and gamma ray radiation is of concern both for public health and radiation standard-setting, the only valuable quantitative information available to estimate this risk is derived from populations with acute and largely high-dose exposures. These estimates are subject to uncertainties associated with the assumed shape of the dose-response function used for downward extrapolation of risk.

The existence, since 1926, of a professional registry of over 170,000 medical x-ray technologists offered a unique opportunity to study a large and well-defined population occupationally exposed to highly fractionated low-dose radiation. The two most sensitive organ sites for radiation carcinogenesis in women, the breast and the thyroid, are being evaluated. Preliminary results from some 80,000 responses to a mail questionnaire suggest a twofold risk of thyroid cancer.

Cancer incidence among 27,011 diagnostic x-ray workers was compared to that of 25,782 other medical specialists employed between 1950-1980 in China. X-ray workers had a 50% higher risk of developing cancer than other specialists not frequently exposed to radiation during employment. Cancers linked to radiation work included leukemia, breast and thyroid, and possibly bone and skin. High risks of cancers of the esophagus and liver were not consistent with a radiation effect and might reflect differences between groups of hospital workers in social class, alcohol intake, dietary habits, and other risk factors. The excess leukemia followed a wave-like pattern, peaking 10-14 years after start of employment and decreasing to normal levels after 20 years. No excess lung cancer or multiple myeloma was observed.

Studies to evaluate cancer mortality among radiation workers are ongoing. Preliminary results from one investigation suggest that the dosimetry records from a large commercial company may be useful in evaluating the long-term health effects of chronic occupational exposure to radiation. Cumulative doses as high as several hundred rad among workers were identified, and record-linkage with the National Death Index was able to identify deaths occurring since 1979. A study of workers at one nuclear power plant developed a feasible, although labor intensive, approach to obtain cumulative radiation doses for both utility and contract employees. However, the results demonstrated the need for the Nuclear Regulatory Commission to consider a modification of their reporting requirements to include annual doses with personal identifiers. If changed, a registry of radiation workers could be effectively created.

Approximately 2,000 women in China were evaluated for nodular thyroid disease by physical examination. Women residing in areas of high natural background radiation due to radioactive monazite sands were not found to have a higher prevalence of thyroid nodules or cancer than women residing in other areas of southern China. The cumulative dose to the thyroid was estimated to be between 8 and 18 rad, and the absence of any differences suggests that protracted exposures to very low levels of ionizing radiation throughout life are not associated with a detectable increase in thyroid nodular disease.

Radon exposure in the home has been suggested as an important risk factor for lung cancer, and collaborative case-control studies are ongoing in New Jersey, Missouri, Sweden and China. Lung cancer mortality in the Reading Prong is being

evaluated in terms of geologic characteristics related to increased radon gas levels in residences. Comparisons of measurements made in Swedish dwellings showed a good correlation between thermoluminescence dosimeters placed in dwellings for two weeks, and alpha track detectors placed in dwellings for six months and for one year. However, seasonal variations were such that for the purpose of risk assessment in epidemiologic studies, measurements for a whole year may be preferable to those for shorter intervals.

A study of mortality in the vicinity of nuclear installations in the U.S. was initiated in light of recent reports suggesting an increased risk of childhood leukemia associated with living close to similar facilities in England. All installations that were ever operational and that exceeded nominal power output have been selected. Mortality in counties with or near these plants will be compared with mortality in counties with similar demographic and socioeconomic characteristics.

Drug Studies: This project focuses on the long-term health effects of drugs, especially therapeutic agents, as they may apply to carcinogenicity. Patients treated in randomized clinical trials have been studied, resources of the Surveillance, Epidemiology, and End Results (SEER) Program have been employed, and collaborative studies have been initiated with several institutions. In collaboration with NCI's Environmental Epidemiology Branch and the Division of Cancer Treatment, a systematic study of therapeutic drugs continues. Occasionally, it has been possible to evaluate other drug exposures in populations that have been studied primarily for other reasons.

A study of women treated with melphalan or chlorambucil for ovarian cancer in five randomized clinical trials previously found a very high risk of leukemia. This study was expanded to include patients treated at the Mayo Clinic and at the M. D. Anderson Hospital. Comparative analyses indicated that the leukemic potential of cyclophosphamide is significantly lower than that of melphalan. These data are being combined with data from breast cancer clinical trials to evaluate more clearly the patterns of leukemia risk by time, age, dose and other factors. Studies of low-dose adjuvant chemotherapy did not find an increase of leukemia following exposure to antimetabolites such as 5-fluorouracil (5-FU). Ongoing studies include the evaluation of patients with colorectal cancer and lung cancer who have received nitrogen mustard, cytoxan, methotrexate, and lomustine in the Veterans Administration clinical trials system; and an evaluation of patients treated with triethylenethiophosphamide and 5-FU in early clinical trials of breast cancers.

A case-control study of 220 children with second malignant neoplasms and 400 controls is currently being analyzed to evaluate the relationship between therapy received for the first malignant neoplasm and the development of the second cancer. These children were treated with a wide range of chemotherapeutic agents. Alkylating agents were found to be associated with a fourfold risk of subsequent bone cancer, suggesting, for the first time, that chemotherapy may increase the risk of solid tumor development among long-term survivors of childhood cancer.

Among 12,000 patients known to have received chemotherapy for the treatment of breast cancer and reported to the SEER registries, a ninefold increased risk of acute nonlymphocytic leukemia was found. The increased risk of leukemia first appeared two years after the breast cancer diagnosis, was highest in 5-year

survivors, and was concentrated in patients with regional node involvement. Among women diagnosed with breast cancer before the era of adjuvant chemotherapy (1973-1974), no excess leukemias were observed (RR=1.1). A detailed case-control study is being conducted in Connecticut, Iowa, Detroit, Los Angeles, and Atlanta to clarify the possible association of leukemia and preleukemia among breast cancer patients treated with adjuvant chemotherapy. The leukemia risk for the two most frequently used alkylating agents, melphalan and cyclophosphamide, will be quantified and compared, and the dose-response relationship will be estimated. Results from a feasibility study in Connecticut indicate an 11-fold increased risk of acute leukemia and preleukemia after alkylating agent therapy and suggested a higher risk for melphalan than for cyclophosphamide.

The SEER registries are being used to examine the risk of second tumor development associated with various treatments for the primary cancer. In particular, solid tumors appearing five or more years after initial treatment with alkylating agents for 17 primary cancers are being evaluated for possible detailed field investigation.

Commonly used drugs, e.g., oral contraceptives, menopausal estrogens, antihistamines, sleeping pills, antibiotics, and medicine for severe diarrhea, were not found to be related to thyroid cancer in a population-based case-control interview study. A study continued of epileptic patients and their offspring to evaluate the possible transplacental carcinogenicity of anti-convulsive drugs. The possible late effects following isoniazid therapy for pulmonary tuberculosis will be evaluated further in large-scale mortality studies in Connecticut and Massachusetts.

Multiple Primary Cancer Studies: The Branch conducts a variety of studies to evaluate the risk of developing a second malignant neoplasm following treatment for an initial primary cancer. Such studies are conducted to evaluate treatment effects, generate hypotheses about common etiologies and provide insights into mechanisms of carcinogenesis. The SEER program and other cancer registries have been used to identify second primary cancers in persons with initial cancers of the breast, testis, endometrium, kidney, and cervix. Patients with cutaneous T-cell lymphoma were found to be at significant risk of developing a second cancer (RR=1.7). Excesses of lung cancer may have been due to an altered immune status; increased colon cancers may provide clues to common exposures or susceptibility mechanisms.

Laboratory Studies: A number of cytogenetic studies have been added to epidemiologic investigations to determine the usefulness of somatic cell chromosome aberrations in circulating lymphocytes as biological dosimeters following partial body radiation exposure. Cytogenetic aberration data are being evaluated in five medically irradiated populations in collaboration with the Oak Ridge Associated Universities. The objectives are to determine the type and frequency of chromosome aberrations and to compare dose-response relationships with those seen in A-bomb survivors who experienced total body exposures; and to determine the persistence of effects in relation to sex, age at exposure, dose, dose fractionation, and radiation quality. Populations being evaluated include persons irradiated for enlarged tonsils or thymic glands as children, cervical cancer patients treated with radiation, tuberculosis patients who received multiple chest fluoroscopies and women irradiated for benign gynecologic disorders. A small, but statistically significant, increase in

translocations and inversions was found in tonsil patients treated by radiotherapy when compared with those treated by surgery. Large differences in the frequency of similar aberrations were found between exposed and nonexposed cervical cancer patients. Among persons irradiated for enlarged tonsils, serum tests and measurements of thyroglobulin concentrations have been made, including T3, T4, TBGI, calcium, thyroid stimulating hormone and antimitochondrial antibody. To evaluate an unusual lowering of breast cancer risk among postmenopausal women following ovarian and adrenal irradiation for cervical cancer, serum determinations of hormones (estrone, estradiol, testosterone, and androstenedione) are being made. Cultured skin fibroblasts from two irradiated populations are being obtained to evaluate the possibility that abnormal in vitro sensitivity to ionizing radiation, indicating an impaired ability to repair damaged DNA, might be associated with an enhanced risk of radiogenic cancers. Populations studied include the atomic bomb survivors and the Israeli patients irradiated for ringworm of the scalp. A study is continuing among atomic bomb survivors of the relationship between cancer induction and levels of hormones and micronutrients in sera obtained prior to cancer diagnosis.

Studies of cervical cancer patients found a significant dose-dependency with increasing bone marrow dose for stable but not for unstable chromosome aberrations. Increased aberrations were detected up to 35 years after exposure, indicating that radiation damage can persist for extremely long periods of time. Overall, the percent of aberrant chromosomes was much lower than expected based on data from the atomic bomb survivor study. However, when adjustment was made for cell-killing effects within the high-dose pelvic area, the chromosome aberration frequencies and percent aberrations per unit dose overlapped for cervical cancer patients and atomic bomb survivors. These data thus provide additional confirmation that the very low risk of leukemia in cervical cancer and other patients given localized high-dose radiotherapy is the result of cell-killing effects of radiation.

Methodologic Studies: This project area focuses on methods for increasing the information from existing bodies of data and for treating analytic problems that arise during the course of other studies. For cancer sites for which a wealth of epidemiologic data exists, attempts are made to resolve apparent inconsistencies among different studies and to strengthen inferences. This is accomplished by working in collaboration with the original investigators and by reanalyzing the basic data in parallel, using identical stratifications with respect to age at exposure, length of follow-up, and identical assumptions with respect to dose-response models and latent period. Such an approach is being applied to breast cancer incidence data and to thyroid cancer incidence data from several exposed populations.

Special problems of estimating cancer risk from low-dose exposures to ionizing radiation have been explored, including statistical power, sample size, and dose-response model assumptions. Bayesian models have been considered for incorporating information from experimental radiobiology. Random error in individual dose estimates was found to bias dose-response analyses based on grouped data. The proportional hazards method was adapted to a factorially designed, long-term, animal experiment to assess possible interactions between radiation and other carcinogens in the induction of mammary tumors. Breast cancer risk among A-bomb survivors has been explored using new models in which the temporal distribution of baseline and excess risk are compared as well as integrated risk over the entire period of observation. New statistical methods

were developed to analyze interaction between radiation and other risk factors in a case-control study of breast cancer in which cases and controls were matched on radiation dose. A package of epidemiologic programs for personal computers is nearing completion. Several of these programs were used by the National Academy of Sciences BEIR IV committee in their analyses of the risks associated with radon exposure, and they are currently being used by the BEIR V committee as the primary tool for the analysis of data from a wide variety of studies of radiation effects.

An interactive computer program for confidence interval estimation of log-normal means has been written for personal computers and is among the tools being used by NCI and Department of Energy collaborators in uncertainty analyses of fallout doses for persons living downwind of the Nevada Test Site at the time of above-ground atomic bomb testing in the U.S.

The risk of radon-induced lung cancer among residents of single family homes in the U.S. was estimated using models recently developed by the National Academy of Sciences BEIR IV Committee. These models predict that approximately 9% of all lung cancer deaths (about 12,700 deaths per year) may be due to indoor radon exposure. The attributable risk is highest among men and among smokers. Most of the contribution to the attributable risk arises from exposure rates below 4 pCi/l for which no remedial action is recommended.

Reviews: A major role of the Branch is to continue to provide comprehensive and critical reviews of the health effects of ionizing radiation. Such reviews include a review of cancers following medical irradiation, an overview of risks associated with radioactive wastes, an evaluation of the statistical and epidemiologic issues concerning estimation of cancer risk from low doses of ionizing radiation, a review of the possible risks of radiotherapy for breast conservation treatment, and overviews on the importance of latent period, risk projection and time-response models in estimating cancer risks. These critical reviews help the Branch stay current in the area of radiation carcinogenesis and suggest new directions for the research programs.

OTHER ACTIVITIES:

The Branch continues to advise and collaborate with other agencies and individuals involved in radiation research and regulatory activities. Branch members have served as consultants or committee members for the National Council on Radiation Protection and Measurements, the Department of Energy, the Department of Defense, the Oak Ridge Associated Universities, the Environmental Protection Agency, the DHHS Subcommittee to Coordinate Federal Radiation Activities, the National Aeronautics and Space Administration, the International Commission on Radiation Protection, and the World Health Organization, among others. At times staff members have become heavily involved in controversial public policy issues and debates, most recently with the issue of possible cancer risk associated with living near nuclear installations in the United States.

In collaboration with NCI's Biostatistics, Clinical Epidemiology and Environmental Epidemiology Branches, the Radiation Epidemiology Branch continues to identify and utilize epidemiologic resources best available at the national or international level. Cost-efficient methods for tracing persons exposed to carcinogens in the past have been evaluated, and various state and national

record systems have been used for epidemiologic purposes (e.g., Social Security Administration (SSA), Internal Revenue Service (IRS), National Center for Health Statistics, Health Care Finance Administration, U.S. Postal Service, Veterans Administration, and various state departments of vital statistics). Efforts continue to be made to persuade the Nuclear Regulatory Commission to establish a registry of radiation workers that could be used to investigate the effects of exposure to ionizing radiation. Initiatives to develop and coordinate national data resources continue to be made that, with appropriate safeguards, may be tapped by qualified investigators throughout the country. Efforts continue to extend, retroactively, coverage of mortality before 1979 when the National Death Index began. Progress was made in obtaining from the SSA essential information for follow-up studies, and IRS agreed to change its agreement with the National Institute for Occupational Safety and Health under which IRS addresses are provided for occupational studies--the changes making it possible for SSA to furnish social security numbers needed to search the IRS address file. Research using Veterans Administration hospital indices is underway, and mortality follow-up of veterans who completed questionnaires in the 1950s on smoking and occupation continues.

To utilize, more fully, resources that are available in cancer registries in the United States and other countries, collaborative record-linkage studies have continued. The Branch also provides on-the-job training of staff at the postdoctoral level, supervises graduate students during NIH summer training programs, provides field research opportunities for doctoral candidates at schools of public health, and collaborates with visiting scientists from a number of countries, including Denmark, Germany, Sweden, Israel, Japan, Canada, the Netherlands, and the People's Republic of China.

New directions and ongoing research projects of the Radiation Epidemiology Branch undergo critical review. Oversight and evaluation are provided through weekly Branch meetings; monthly meetings with support services groups; frequent contact with other support services and collaborating groups; several working groups (e.g., drug studies); interagency committees; formal review mechanisms for the careful scrutiny of questionnaires and protocols by internal and external review committees; ad hoc external review groups for major studies (e.g., the International Radiation Study of Cervical Cancer Patients); and a variety of advisory bodies that oversee Institute activities, notably the Board of Scientific Counselors of the Division of Cancer Etiology.

SUMMARY REPORT

RADIATION EPIDEMIOLOGY BRANCH

PROGRESS ON RESEARCH CONTRACTS

The studies of radiation-induced cancers supported by the research contract mechanism (24 contracts) are to strengthen the quantitative basis for risk estimation, especially at low doses, to improve the understanding of the role of host and environmental factors on radiogenic cancer risk, and to provide insights into carcinogenic mechanisms. Specific studies are discussed below.

Radiation Risk Estimation in Israeli Children Irradiated for Tinea Capitis. The objectives of this study are to determine the incidence of cancer in 10,000 Israeli children irradiated for ringworm of the scalp, 10,000 nonexposed persons selected from the general population, and 5,000 nonexposed siblings. The methods employed are as follows. The study cohorts were previously identified from population records (1949-60) and the risk of thyroid cancer evaluated. Medical records in all 22 Israeli hospitals and records available in the Central Tumor Registry have been searched to determine malignant and benign tumors that developed in the exposed and comparison cohorts. Detailed dosimetry data have been obtained. Death certificates have been evaluated for those who have died, and the vital status as of 1981 has been determined for all enrolled persons. Malignancies of particular interest include thyroid, brain, parotid gland, breast, bone, lung, esophagus, larynx, skin, leukemia, and lymphoma. A preliminary report has indicated that increased rates of malignant (35 vs. 8.7 expected) and benign tumors of the thyroid, tumors of the nervous system (66 vs. 8.6), and leukemia (13 vs. 4.7) are associated with scalp irradiation during childhood. A paper on the mortality experience of these children has been published in the American Journal of Epidemiology. A paper on radiation-associated neural tumors has been submitted for publication. The concomitant high relative risk of radiogenic thyroid cancer among Israelis born in North Africa and high prevalence of ataxia telangiectasia heterozygosity in this population suggested the possibility of an enhanced host-susceptibility. As such, a 2-year extension of a biochemical epidemiologic study was continued in collaboration with the Clinical Epidemiology Branch. Cultured skin fibroblasts are being obtained to evaluate whether abnormal in vitro sensitivity to ionizing radiation, indicating an impaired ability to repair damaged DNA, might be associated with an enhanced risk of radiogenic cancers. Further evaluation of radiogenic skin cancer in this population will be conducted.

Cancer in the Opposite Breast Following Radiotherapy for Primary Breast Cancer. The objectives of this study are to determine whether radiotherapy for breast cancer increases the risk of a second primary breast cancer in the contralateral breast, and, if such a risk exists, to evaluate the dependence of risk on dose and age at exposure. Study subjects have been drawn from approximately 50,000 women with breast cancer reported to the population-based tumor registry in Denmark between 1943-1975. Cases are all women with breast cancer who developed a second primary breast cancer ten or more years after treatment for the first malignancy. Controls are women with a primary breast cancer who did not develop another breast cancer. One control has been matched to each case on age

at initial breast cancer diagnosis, calendar year of diagnosis, and survival time. Approximately 1,000 cases and 1,000 controls are available for study. Individual dosimetry determinations are being made. Record abstraction is continuing.

Cancer Risk in Patients Irradiated for Peptic Ulcer. The objectives of this study are to determine the risk of cancer in 2,054 patients treated by x-rays for peptic ulcer at the University of Chicago between 1937-1965, compared with 2,500 patients treated by surgery or other means during the same time period. Hospital and radiation therapy records are being used to identify the study cohorts. For those patients treated by x-rays, estimates of radiation doses to specific organs will be determined. Death certificates will be obtained for those who have died and the vital status, as of 1984, will be ascertained. Malignancies of particular interest include the stomach, pancreas, colon and lung, and leukemia.

A Follow-up Study of Patients Treated for Hyperthyroidism. The objective of this study is to determine cancer and other causes of mortality in a cohort of 21,000 patients treated by 131-I for hyperthyroidism between 1946-1964. Mortality rates in the exposed cohort will be compared with those among 10,500 patients treated by thyroid surgery. This is the second follow-up study of a population identified in 18 hospitals in the U.S. and one in England followed from 1961-1968. Radiation dosimetry estimates will be derived from the 131-I treatment records. This study is being conducted in four geographical areas of the U.S. (California, New York, Boston, and other U.S. areas, mainly in the midwest) and in Sheffield, England. Malignancies of particular interest include thyroid, breast, salivary glands, leukemia, kidney and bladder. Record abstraction has been completed and location activities are ongoing.

Thyroid Cancer Risk Following Diagnostic and Therapeutic 131-I Exposure. The objectives of this study are to determine the risk of thyroid cancer and other cancers following diagnostic and therapeutic 131-I exposure. This study is an extension and expansion of a previous study in Sweden. The new investigation includes additional Swedish hospitals where 131-I was administered and extends patient follow-up. Over 40,000 patients exposed to diagnostic 131-I between 1950-1970 have been identified in seven hospital centers in Sweden. Approximately 20,000 patients treated by 131-I for hyperthyroidism and 6,000 patients treated by 131-I for thyroid cancer between 1951-1975 have been identified at these same seven centers. Medical and therapy information are being abstracted from the patient hospital record. Follow-up is being conducted by record linkage with the Swedish Cause of Death Register (1951-1985) and the Swedish Cancer Registry (1958-1985). Malignancies developing in the first 7 years of study (1951-1957) are being identified through death certificates. Expected numbers of malignancies will be calculated using age-, sex-, site-, and calendar-time-specific-incidence data from the Cancer Registry or on the basis of mortality rates from the National Office of Vital Statistics. A manuscript on the population of patients receiving diagnostic 131-I has been prepared. There was no evidence of an increased risk of thyroid cancer among 10-year survivors.

Risk of Cancer in X-Ray Technologists. The objective of this study is to evaluate the long-term effects of chronic low-dose occupational exposure to radiation among 145,000 radiologic technologists certified for at least two years by the American Registry of Radiologic Technologists since its inception

in 1926. Optical scan questionnaires were sent to all active members and to about 25,000 inactive members who have been located to determine cancer incidence and to obtain information on the use of dosimeters and cancer risk factors, such as cigarette smoking. Nearly 90,000 questionnaires have been returned to date. Telephone follow-up is being attempted with nonrespondents to encourage their participation. While on the phone, cancer incidence is being ascertained. Various methods and resources are being used to trace the 6,000 inactive members as yet unlocated. Death certificates are being procured for about 3,700 deceased subjects. Cancers reported on questionnaires or death certificates are being histologically confirmed. Preliminary findings suggest higher than expected incidence of thyroid and endometrial cancers. Quantitative estimates of radiation exposure are being made for all questionnaire respondents based on length of employment, types of procedures performed, and personal diagnostic and therapeutic x-ray exposures. Record linkage with dosimetry files of a national company have also been made. Excess cancer incidence and mortality will be evaluated in relation to radiation exposure. Additionally, nested case-control studies have been undertaken to make direct quantitative evaluations of the relationships between radiation exposure and occurrence of leukemia, and cancers of the breast, thyroid, and lung. For cases of these cancers and appropriately matched controls, actual occupational radiation exposures, derived from film badge readings, are being ascertained from employers and from the nation's largest dosimetry company. One manuscript has been published, and another has been drafted for publication which describes the methodology and descriptive population characteristics.

Epidemiologic Studies of Cancer among A-bomb Survivors. The objectives of this collaborative study are to identify and quantify the possible roles of radiation and other environmental and host risk factors in the development of certain cancers and to carry out other studies of cancer risk among members of the A-bomb survivor population. Investigations based on the life span study sample of 94,000 A-bomb survivors and 26,000 nonexposed individuals, and a clinical subsample of 12,000 survivors and controls are carried out at the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan. All studies involving new or unpublished data are collaborative and include investigators from NCI, RERF, and outside organizations as required; collaboration is facilitated by personnel exchanges between RERF and NCI. Methods include cohort studies of cancer incidence as determined from death certificates, tumor and tissue registries, searches of hospital and clinical records, and case-control interview studies in which epidemiologic factors other than radiation, as determined from existing records or by interview, are investigated. Reviews of diagnostic material by panels of pathologists are often employed in connection with the studies. Stored blood sera obtained prior to cancer diagnosis may be analyzed to investigate possible influences of hormonal, nutritional, and other factors. A major long-term goal of the project is to investigate ways of improving the completeness and diagnostic accuracy of cancer case ascertainment materials through the linkages with tumor and tissue registries, insurance records, contacts with hospitals and physicians, and other means.

A study of female breast cancer incidence has been published. A manuscript on colorectal cancer incidence has been prepared and is undergoing review at RERF and at NCI prior to being submitted for journal publication. Case-control interview studies of breast, colorectal, and thyroid cancer are in various stages of completion. Stored serum samples from cancer cases and controls,

obtained in 1971-73, 5 or more years before cancer diagnosis, have been assayed for hormonal and micronutrient content. Chromosomal materials are being exchanged between RERF and a contractor at Oak Ridge Associated Universities to investigate comparability of chromosomal aberration assays of medically irradiated populations under investigation by the Branch with those of A-bomb survivors studied at RERF. A pathology review of diagnostic material from high-dose and low-dose lung cancer cases from the A-bomb survivors and from U.S. uranium miners has been conducted by a binational panel, and the results are being analyzed to see if there are consistent patterns with respect to country, radiation dose, smoking history, and type of radiation exposure. A major step toward the goal of improving the ascertainment of cancer risk in the A-bomb survivor population was taken with the acceptance by RERF and its Board of Scientific Counselors of a platform protocol, prepared by collaborating investigators in the Branch and at RERF, for studies of cancer incidence. The approach is modelled on that of the successful collaborative study of breast cancer incidence, and involves participation by Hiroshima and Nagasaki pathologists in addition to investigators from RERF and NCI. It also involves attempts to ascertain incident, non-fatal cases among RERF sample members who no longer reside in the two cities.

The following findings have been obtained: Breast cancer risk is strongly related to radiation dose for exposures at all ages prior to (about) 40, but not at older ages; the existence of an excess risk following exposure in early childhood was not known previously. For women exposed to similar radiation doses at similar ages, the likelihood of subsequent cancer was more than twice as high if no pregnancy had occurred by the time of exposure than for parous women. Regardless of reproductive status at the time of exposure, radiation-induced breast cancer was less likely among women who experienced their first deliveries at young ages, who had many children, or who had lengthy lactation histories. Colon cancer risk is strongly related to radiation dose, especially for cancer of the sigmoid colon. Interview data confirm that high exercise levels are associated with reduced colon cancer risk, although not necessarily with reduced risk of radiation-induced colon cancer.

Prenatal X-ray Exposure and Childhood Cancer in Twins. The objective of this study is to evaluate the relationship of prenatal x-ray exposure to subsequent incidence and mortality from cancer before the age of 16 years. Twins are especially suitable subjects for this study because, until recent times, women thought to be pregnant with twins were often x-rayed regardless of other medical indications for this procedure. Comparisons of prenatally x-rayed single-born subjects are thought to be confounded with the medical complications of pregnancy for which the radiologic investigation had been made. Twins are also suitable subjects because the high frequency of prenatal x-ray exposure leads to a better statistical power of the comparison of exposed and nonexposed subjects for subsequent medical events in samples of limited size.

The study objectives can be carried out efficiently in Sweden because of the unique record resources there. A registry of 55,000 twin births from 1926 to 1967 is being maintained by the National Institute of Environmental Medicine. Centralized, computer-based files of deaths since 1950 and of cancer registrations since 1958 are available. Individuals can be traced through central population registration and through a network of parish offices. A national health service system provides a means of obtaining lifetime records of medical care for selected study subjects.

About 100 cases of childhood cancer and 200 comparison subjects have been identified for study and their medical records and those of their mothers have been reviewed. This sample size is sufficient to detect a doubling of risk with a high probability. Information obtained is being prepared for analysis which will include the number and kind of x-ray exposures, stage of pregnancy at exposure, birth weight, duration of gestation, medical complications of pregnancy, and other variables that might confound the comparison. The material will also provide a means of comparing overall childhood cancer incidence among twins with that of single-born subjects, which is also relevant to the main objectives of this investigation.

Irradiation for Benign Menstrual Disease. The objectives of this study are to determine cancer incidence and mortality and estimate the risks of radiation-induced cancer in women treated for benign gynecological disorders (BGD). A study size of at least 9,000 exposed women should be sufficient to provide adequate statistical power to detect and evaluate dose-response relationships for radiogenic leukemia and solid tumors. Medical, therapeutic, and follow-up information has been abstracted from medical records in New York, Massachusetts, Connecticut, Rhode Island, and Sweden. Death certificates have been obtained for those who died, and questionnaires have been sent to those who are alive. Collaborative mortality analyses are currently underway and comparisons are being made with Connecticut population rates for cancer incidence and with women treated without radiation for BGD. Organ-specific radiation doses have been determined for individual BGD patients. A summary of a workshop held to discuss this collaboration was published in the Journal of the National Cancer Institute. Reports on dose response and organ-specific cancer risk are being prepared.

Leukemia and Lymphoma Associated with Diagnostic X-Ray. The objective of this study is to quantify the risks of adult leukemia and lymphoma associated with radiation exposure from diagnostic x-rays. Using the resources of the Kaiser prepaid health plans in Oakland, California and Portland, Oregon, approximately 1,256 leukemia and lymphoma cases were found diagnosed since the inception of these plans in the early 1940s. At least one matched control has been identified for each case (1,578 in total). Complete medical record information on diagnostic x-ray exposures and other cancer risk factors have been abstracted for all subjects from Oakland and Portland. Diagnostic x-ray exposures were converted to total radiation doses received by the active bone marrow, using estimates of exposure for x-ray procedures provided by an expert medical physicist from M. D. Anderson Hospital. Data from Portland and Oakland were consolidated and analyses completed. (The contracts with the Kaiser Foundation Research Institute in Oakland [NO1-CP-41058] and Portland [NO1-CP-41059], are listed under the Environmental Studies Section, Environmental Epidemiology Branch, Epidemiology and Biostatistics Program, Division of Cancer Etiology.) An abstract was prepared for the annual meeting of the Society of Epidemiologic Research. No association was found with chronic lymphocytic leukemia. For all other leukemias combined, there was a significant increase in risk with increasing number of x-rays but the trend diminished when x-rays near the time of diagnosis were excluded. The same pattern was seen for non-Hodgkin's lymphoma.

Cancer Risk Following Multiple Chest Fluoroscopies During Cardiac Catheterization in Childhood. The objective of this cohort, record-linkage study is to evaluate the risk of cancer in 1,050 Israeli children who underwent cardiac catheterization between 1950-65. A roster of these patients with detailed exposure information are being matched to vital statistics records and the Israeli Cancer Registry. Linkage is by Population Identification Number. Of particular interest will be the risk of leukemia, thyroid, and breast cancer.

Leukemia and Preleukemia Following Chemotherapy for Breast Cancer. The objectives of this project are to determine, in a population-based study, whether chemotherapy for breast cancer increases the risk of subsequent leukemia and preleukemic conditions, and to quantify and compare the leukemia risk for the two most frequently used alkylating agents, melphalan and cyclophosphamide. Record linkage studies in five population-based cancer registries (Connecticut, Iowa, Detroit, Los Angeles, and Atlanta) have identified 108 cases of women with breast cancer who developed subsequent leukemic disorders. Three controls for each case have been selected from a pool of breast cancer patients who did not develop a second cancer. Complete treatment histories are being abstracted from hospital charts and physician records. If sufficient data are available, the dose-response relationship will be examined.

Cancer Risk in Epileptics and Their Offspring Following Anti-Convulsive Drug Exposure. A study has been completed of epileptic patients who received phenobarbital, dilantin, and other anti-convulsive drugs to evaluate possible carcinogenicity, particularly in offspring exposed in utero. Cancer registry records in Denmark have been linked with hospital lists to ascertain cancers. The risk of cancer in the epileptics is being correlated with any past exposure to thorotrast which would accompany cerebral angiography. A preliminary cohort investigation has been conducted. Data analysis are ongoing.

Study of Thyroid Cancer and Nodularity in High Radiation Background Areas in China. The pilot was successful and a full-scale study was initiated. Over 2,000 women were examined to learn whether cumulative lifetime exposure to high background radiation is associated with a detectable increase in thyroid disease in China. Analysis of examination findings and blood studies, including chromosomal data is ongoing. A meeting of Chinese and U.S. collaborators will take place this year to discuss study findings.

Study of Cancer Risk in Women Treated with Radiation for Infertility. Cancer incidence in a cohort of 1,200 Israeli women who received pituitary and/or ovarian x-ray therapy in the 1940s for the treatment of infertility and menstrual disorders is being evaluated. Subject identification, data abstraction, subject tracing and record-linkage techniques with the Israeli Cancer Registry have been completed. Hypotheses of principal interest include the effects of hormonal infertility on breast and ovarian cancer and the effects of low-dose irradiation on the development of brain and thyroid cancers in women of reproductive age.

Study of Radiation Workers with Individual Dosimetry Determinations. An evaluation is underway to determine the usefulness of the Landauer dosimetry records for possible study of the long-term effects of chronic exposure to radiation experienced because of occupation. A sample of workers over the age of 40 years who terminated their dosimetry service between 1977-1983 has been selected. Each occupational group (government, medical, nuclear power, other

industry, and education) has been included in equal portions. Approximately 1,000 persons in each category are being evaluated as to the completeness of their dosimetry records. Gaps in employment histories and dosimetry measurements are being evaluated. The sample has been linked to both the Social Security Administration death files and the National Death Index. Death certificates will be obtained, and the number of deaths in this sample determined.

Leukemia Following Radiotherapy for Uterine Corpus Cancer. The objective of this study is to quantify the relationship between radiation dose and leukemia induction in a population of women treated for uterine corpus cancer. An estimated 200 cases of leukemia following uterine corpus cancer and 880 matched controls with cancer of the uterine corpus will be identified from 9 population-based cancer registries in the United States, Canada and Europe utilizing the record-linkage Master Agreement mechanism. Medical records will be abstracted and radiation dose records photocopied for each study subject. Leukemias will be reviewed and reclassified by the study hematologist. Radiation dose to the active bone marrow will be estimated for 14 segments of the bone marrow. Generalized relative risk functions will be fit to the data to describe the dose-response relationship, and the results will be compared to risk estimates obtained from the Cervical Cancer Study using the linear-exponential and quadratic-exponential risk models. Of particular interest in this study will be a comparison of the effect of dose fractionation from external beam therapy with the effect of continuous exposure from brachytherapy. In addition, the pattern of radiation-induced leukemia risk will be examined by time since initial treatment, and age and calendar year of exposure.

RADIATION EPIDEMIOLOGY BRANCH

RESEARCH CONTRACTS ACTIVE DURING FY 88

Institution/Principal Investigator/ Contract Number	Title
Chaim-Sheba Medical Center Baruch Modan NO1 CP 01042	Radiation Risk Estimation in Israeli Children Irradiated for Tinea Capitis
Chicago, University of Melvin L. Griem NO1 CP 41011	Cancer Risk in Patients Irradiated for Peptic Ulcer
Connecticut Department of Health Services Maria J. Schymura NO1 CP 51041 01	Leukemia Following Radiotherapy for Uterine Corpus Cancer
Danish Cancer Registry Hans H. Storm NO1 CP 51055 04	Leukemia Following Radiotherapy for Uterine Corpus Cancer
Danish Cancer Registry Hans H. Storm NO1 CP 51037	Cancer in the Opposite Breast Following Radiotherapy for Primary Breast Cancer
Danish Cancer Registry Jorge Olsen NO1 CP 51055	Cancer Risk in Epileptics and Their Offspring Following Anti-Convulsive Drug Exposure
Emory University Raymond Greenberg NO1 CP 51054	Leukemia and Preleukemia Following Chemotherapy for Breast Cancer
Energy, Department of Brookhaven National Laboratory A. Bertrand Brill Y01 CP 40503	Thyroid Disease Following 131-I Therapy for Hyperthyroidism
Harvard University Richard R. Monson NO1 CP 31049	Cancer Risk in Women Irradiated for Benign Gynecologic Disorders
Harvard University Richard R. Monson NO1 CP 41060	A Follow-up Study of Patients Treated for Hyperthyroidism
Health Research, Inc. Diane Cookfair NO1 CP 31048	Cancer Risk in Women Irradiated for Benign Gynecologic Disorders

Israeli Cancer Registry Leah Katz NO1 CP 51047	Cancer Risk Following Multiple Chest Fluoroscopies During Cardiac Catheterization in Childhood
Karolinska Institute Lars-Erik Holm NO1 CP 51034	Thyroid Cancer Risk Following Diagnostic and Therapeutic 131-I Exposure
Laboratory of Industrial Hygiene Beijing, China Wang, Zuoyuan NO1 CP 61018	Study of Thyroid Cancer and Nodularity in High Radiation Background Areas in China
Memorial Hospital for Cancer and Allied Diseases David Schottenfeld NO1 CP 41061	A Follow-up Study of Patients Treated for Hyperthyroidism
Michigan Cancer Foundation Ann Grossbart Schwartz NO1 CP 51050 01	Leukemia and Preleukemia Following Chemotherapy for Breast Cancer
Minnesota, University of Jack S. Mandel NO1 CP 21015	Risk of Cancer in X-Ray Technologists
National Academy of Sciences Charles Eddington NO1 CP 01012	Epidemiologic Studies of Cancer Among A-bomb Survivors
National Institute of Environmental Medicine Anders Ahlbom NO1 CP 51033	Prenatal X-ray Exposure and Childhood Cancer in Twins
Ontario Cancer Treatment Foundation Eric J. Holowaty NO1 CP 51047 01	Leukemia Following Radiotherapy for Uterine Corpus Cancer
Southern California, University of Leslie Bernstein NO1 CP 51035 02	Leukemia Following Radiotherapy for Uterine Corpus Cancer
Southern California, University of Leslie Bernstein NO1 CP 51035 01	Leukemia and Preleukemia Following Chemotherapy for Breast Cancer
State Health Registry of Iowa Peter Isacson NO1 CP 51042 02	Leukemia and Preleukemia Following Chemotherapy for Breast Cancer
State Health Registry of Iowa Peter Weyer NO1 CP 51042 01	Leukemia Following Radiotherapy for Uterine Corpus Cancer

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04481-12 REB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of Radiation-Induced Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. D. Boice, Jr.	Chief	REB	EBP	NCI
Others:	C. E. Land	Health Statistician	REB	EBP	NCI
	Z. Hrubec	Expert Statistician	REB	EBP	NCI
	R. A. Kleinerman	Epidemiologist	REB	EBP	NCI
	E. Ron	Senior Staff Fellow	REB	EBP	NCI
	S. Jablon	Expert Statistician	REB	EBP	NCI
	R. E. Curtis	Statistician	REB	EBP	NCI

COOPERATING UNITS *(if any)*

Radiation Effects Research Foundation, Japan (H. Kato); Department of Energy (R. Goldsmith); Chaim Sheba Medical Center, Israel (B. Modan); Tufts University (M. Kaplan); Harvard University (G. Hutchison)

LAB/BRANCH

Radiation Epidemiology Branch

SECTION

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
11.0	8.0	3.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project (1) examines cancer risk in populations exposed to ionizing radiation, especially at low doses; (2) characterizes risk in terms of dose response, radiation quality, fractionation of dose, time since exposure, sex, age at exposure and at observation, and modifying influences of other environmental and host factors; and (3) examines, tests, and formulates models of radiation carcinogenesis to help define basic mechanisms. Groups studied include the Japanese A-bomb survivors, and populations with therapeutic (e.g., cervical cancer), diagnostic (e.g., tuberculosis), occupational (e.g., x-ray technologists) and environmental (e.g., to radon) exposures. Program members serve on committees advising the government and international agencies.

Results of studies suggest that (1) susceptibility to radiogenic breast cancer declines with increasing age at exposure, the dose response is linear, and risk remains for at least 40 years; (2) repeated exposure to relatively low radiation doses poses some future risk of breast cancer but apparently not lung cancer; (3) high-dose radiation induces fewer leukemias than other types of exposure; cell-killing appears to play an important role in defining dose-response relationships; (4) radiotherapy for cervical cancer also increases the risk of cancers of the rectum, bladder, vagina, stomach and thyroid; (5) diagnostic x-rays may not be causally related to leukemia or lymphoma but simply related to conditions that portend their development;(6) children irradiated for benign conditions are at risk of developing thyroid and brain neoplasia; (7) radiotherapy for breast cancer did not increase the risk of leukemia; (8) radiotherapy for Hodgkin's disease increased the risk of breast cancer; (9) radiotherapy for childhood cancer increased subsequent bone cancer; (10) diagnostic x-ray workers in China are at high risk of leukemia; (11) approximately 9% of all lung cancer deaths may be due to indoor radon; and (12) low-dose radioactiveiodine does not appear to increase the risk of thyroid cancer.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

John D. Boice, Jr.	Chief	REB	EBP	NCI
Charles E. Land	Health Statistician	REB	EBP	NCI
Gilbert W. Beebe	Health Statistician	CEB	EBP	NCI
Ruth A. Kleinerman	Epidemiologist	REB	EBP	NCI
Elaine Ron	Senior Staff Fellow	REB	EBP	NCI
Dale Preston	Expert Statistician	REB	EBP	NCI
Seymour Jablon	Expert Statistician	REB	EBP	NCI
Zdenek Hrubec	Expert Statistician	REB	EBP	NCI
Charles W. Mays	Expert Radiobiologist	REB	EBP	NCI
Rochelle E. Curtis	Statistician	REB	EBP	NCI
Katherine W. Chen	Computer Programmer	REB	EBP	NCI
Michele M. Morin	Epidemiologist	REB	EBP	NCI
Peter Inskip	P-Authority	REB	EBP	NCI
Zhang Shouzhi	Visiting Associate	REB	EBP	NCI
William J. Blot	Chief	BB	EBP	NCI
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Objectives:

(1) To plan and conduct independent and cooperative epidemiologic research to identify and quantify the risk of cancer in populations exposed to ionizing radiation (e.g., x-rays) and nonionizing radiation (e.g., ultraviolet light). Populations with documented therapeutic, diagnostic, occupational, environmental or military exposures are studied; (2) to characterize the risk of radiation-induced cancer in terms of tissues at risk, dose response, radiation quality, fractionation of dose, time since exposure, sex, age at exposure and at observation, and possible modifying influences of other environmental and host factors; (3) to conduct population studies to examine possible analogs of radiation carcinogenesis in man, such as the induction of cytogenetic abnormalities in circulating lymphocytes, and to integrate laboratory markers of radiation exposure and tissue response into epidemiologic studies designed to clarify the patterns of cancer risk and the mechanisms of action; (4) to develop statistical and epidemiologic methodologies to facilitate epidemiologic research and to explore and formulate models of radiation carcinogenesis that may help define basic mechanisms of cancer induction, including the integration of experimental findings with epidemiologic observations; and (5) to advise and collaborate with other agencies and individuals involved in radiation research and regulatory activities.

Methods Employed:

Studies of populations exposed to ionizing radiation are being conducted to strengthen the quantitative basis for risk estimation, especially at low doses, to improve understanding of the role of host and environmental factors on radiogenic cancer risk, and to provide insights into carcinogenic mechanisms.

The relationship between cancer risk and radiation is an especially promising area for epidemiologic research, because quantitative descriptions of exposure are usually straightforward. As Doll has put it, "studies of the quantitative relationships between dose and effect, of the conditions which modify the effect of a specific exposure and of the time relations between duration of exposure, intensity of exposure, length of induction period and the rate of progress of the clinical disease will enable the epidemiologist to take part in formulating and testing hypotheses about the mechanisms by which cancer is produced" (Acta Union Int. Cancer. 20: 747, 1964). The program of radiation studies is summarized in four project areas: Medical Exposures, Atomic Bomb Survivors, Occupational and Environmental Exposures, and Methodologic Studies.

A. Medical Exposures. Studies of populations exposed to medical irradiation have great potential for quantifying late radiation effects because (1) exposures can usually be accurately estimated, (2) nonexposed patients are often available for comparison, (3) useful information on other risk factors can frequently be obtained from existing records, and (4) medical facilities often follow patients for long periods of time after treatment. Radiation studies may be a particularly useful approach to understand the mechanism by which cancer is produced since quantitative descriptions of exposure are usually straightforward, an advantage not available for most other carcinogens. The only evidence that a cancer can be induced by ionizing radiation for relatively insensitive tissues comes from patient populations given high-dose, partial-body, therapeutic irradiation. For other sites, the best evidence of low-dose risk comes from populations given multiple, low-dose, diagnostic irradiation resulting in high cumulative exposures. The radiation studies program tries to assure that maximum benefit is derived from existing epidemiologic resources, and attempts to initiate studies of populations not previously evaluated, but which offer unusual potential for new information. Seventeen medically irradiated populations are currently under study: women irradiated for cervical cancer, uterine corpus cancer, benign gynecologic disorders, infertility, and breast cancer; children irradiated for lymphoid hyperplasia, retinoblastoma and other cancers, or tinea capitis; men irradiated for peptic ulcer; patients who received diagnostic radiographic procedures for tuberculosis, scoliosis, or heart disease; twins who received prenatal x-ray; leukemia and lymphoma patients who received prior diagnostic x-ray examinations; thyrotoxicosis and other patients treated with radioactive iodine; and patients given diagnostic doses of radioactive iodine.

Populations receiving therapeutic irradiation are described below.

1. The International Radiation Study of Cervical Cancer is a program of studies designed to provide new insights into radiation carcinogenesis and to

increase the precision of current risk estimates. These investigations include cohort studies in cancer registries and individual clinics, case-control studies, dosimetry studies, chromosome studies, hormone studies, and pathology evaluations. The program evolved from a WHO-sponsored investigation of 30,000 women treated for cancer of the cervix uteri in nine different countries and clinically evaluated from 1960-1970. The follow-up of most of this population was extended to the present. However, to obtain a sample large enough to measure the effects of relatively low-dose radiation received by organs distant from the site of primary irradiation, the program was expanded through the collaboration of 15 population-based cancer registries. Approximately 200,000 women with cervical neoplasia have been studied. The cancer registry cohort studies have been completed, and detailed case-control studies have been conducted to provide radiation dose estimates on individuals and to evaluate dose response. Changes in serum estrogen and androgen levels, possibly associated with ovarian or adrenal gland irradiation, are being evaluated by radioimmunoassay techniques. Chromosome aberrations in circulating lymphocytes have also been evaluated in relation to total active bone marrow dose.

2. Several studies of childhood irradiation are being conducted. The minimal confounding effect of other carcinogenic influences, such as smoking or occupation, and the possible greater susceptibility of young people to environmental carcinogens, enhances the chances of detecting increased risks due to therapy. The study of 3,000 children treated for enlarged tonsils with radiation or surgery in Boston was completed. Physical examinations were performed on over 1,000 irradiated and surgical patients to determine the risk of thyroid nodules more accurately and to account for the potential detection bias in previous studies where only radiation-exposed persons were screened. Blood studies include the evaluation of serum calcium levels and plasma thyroglobulin concentrations. Chromosome aberrations in circulating lymphocytes are also being investigated to assess exposure more accurately and to evaluate the effect of radiation in causing long-term damage in somatic cells from partial-body exposures..

3. A collaborative study in Israel has continued which evaluates the risk of cancer in 10,000 children exposed to x-rays during the treatment of ringworm of the scalp and in 15,000 comparison individuals. This is a matched prospective cohort study. Malignant and benign neoplasms were ascertained by abstracting pathology records in all 22 hospitals in Israel and through record linkage with cancer and death registries. A biochemical epidemiologic study was developed in Israel to evaluate whether the risk of thyroid neoplasms associated with a low radiation dose (9 rad) might be related to increased host susceptibility associated with heterozygosity for ataxia telangiectasia. Ataxia telangiectasia is a genetic disorder common among North Africans who were also found to be at highest relative risk for radiogenic thyroid disease. Cultured skin fibroblasts will be evaluated for abnormal in vitro sensitivity to ionizing radiation which would indicate an impaired ability to repair damaged DNA. Additional biochemical studies along similar lines have been initiated to evaluate observed excesses of skin cancer.

4. Over 9,000 persons who survived at least 2 years after a diagnosis of childhood cancer in 13 hospitals in the U.S. and other countries have been studied for the risk of second cancer development. Detailed medical records have been abstracted on cases and matched controls to quantify the risks associated with radiation or chemotherapy treatments. Collaborative dosimetry support is being provided for a similar investigation conducted in the United Kingdom.

5. New cohorts of women who received radiotherapy for benign gynecological disorders (BGD) in Massachusetts, New York, Rhode Island, and Connecticut are being evaluated. Cancers of pelvic and abdominal organs, sites which have not been well characterized in terms of radiogenic risk, are being studied. In addition, the paradoxical finding of increased leukemia risk associated with low-dose exposures to the pelvic marrow in BGD patients, but not high-dose exposures in cervical cancer patients, will be investigated, as will the unexpected reduction in breast cancer risk previously associated with irradiation for BGD in postmenopausal women. Chromosome studies are being conducted and findings will be contrasted with data from the international cervical cancer study.

6. Two population-based case-control studies were conducted to evaluate the risk of leukemia in breast cancer patients treated with radiotherapy. In Connecticut, 55 women developed leukemia at least 18 months after a breast cancer diagnosis during the period 1935-1972; two breast cancer controls were matched to each case. A parallel study in Denmark evaluated 129 cases of leukemia following breast cancer and 258 matched controls (1945-1980). Medical records were abstracted and individual bone marrow doses estimated. Analyses of the dose-response relationship between the radiation dose to active bone marrow and subsequent leukemia risk have been completed for the Connecticut study.

7. A study of the carcinogenic effects of radiation therapy for peptic ulcer has continued. Over 2,000 patients who were exposed between 1937-1965 have been identified, and the radiation risks for cancers of the stomach, pancreas, lung, spleen, and kidney will be evaluated and compared with 2,500 patients treated by surgical or medical means. Except for the lung, radiation risks for these sites are not well defined.

8. Cancer mortality in a cohort of 860 women who received pituitary and ovarian x-ray therapy (mean tissue dose: 90 rad and 65 rad, respectively) between 1925 and 1960 for the treatment of infertility and menstrual disorders in New York is currently being evaluated. Hypotheses of principal interest include the effects of hormonal infertility on breast and ovarian cancer and the effects of low-dose irradiation on the development of brain cancers in women of reproductive age. Data collection for a cohort of 1,200 infertile women similarly treated in Israel has recently been completed. Statistical analysis of cancer incidence among the Israeli population is underway.

9. There has been growing concern about the adequacy of the standards presently used to regulate exposures to neutrons. This concern was increased when it was learned that the study of the A-bomb survivors would

yield little information on neutron effects. There are currently no data on the risk of cancer associated with neutron exposures in humans. For this reason, we are exploring the feasibility of conducting a multi-centered epidemiologic study on patients treated with neutron therapy. So far, radiologists from over 15 centers report treating over 8,000 patients. It is estimated that at least 2,000 patients have survived over 2 years and would be eligible for study. A chromosome study of 2-year survivors of neutron therapy is being initiated to evaluate the effects of high LET radiation on somatic cells.

10. A population-based case-control study was initiated among women treated for cancer of the uterine corpus to evaluate the dose-response relationship between radiation dose and the risk of leukemia. Over 220 cases of leukemia following uterine corpus cancer were identified from 9 cancer registries in the United States, Canada, and Europe. Four controls per case were selected among uterine corpus cancer patients who did not develop leukemia. Detailed medical records will be abstracted and the radiation dose to the active bone marrow will be calculated for each study subject.

11. The Surveillance, Epidemiology, and End Results (SEER) cancer registries and the Connecticut Tumor Registry were used to evaluate the risk of breast cancer occurring 10 or more years following radiotherapy for Hodgkin's disease. The effect of age at exposure and time to occurrence were evaluated.

12. To improve and extend the data available on radiogenic thyroid cancer, a previously identified cohort of over 5,000 individuals who received radiation treatment between 1939 and 1960 for enlarged tonsils and other benign conditions of the head and neck is being evaluated. Clinical and radiation therapy data were abstracted from the medical records of 5,054 patients who received at least one course of 200 kVp radiation at Michael Reese Hospital in Chicago. Detailed data regarding method of tumor detection, tumor size and location were abstracted for over 1,000 patients known to have had a thyroid neoplasm. Currently, medical physicists at M.D. Anderson Hospital are estimating organ doses, and we are conducting a pilot study to assess the feasibility of tracing individuals lost-to-follow-up.

13. To derive more understanding of radiogenic thyroid tumors and host susceptibility, we are reanalyzing data from 8 major studies (6 cohort and 2 case-control) of radiation-associated thyroid neoplasia. The basic data are being analyzed in parallel using identical categories and definitions where possible. Additional organ dose determinations are being made by medical physicists so that the analysis will include detailed uniform dose data. The effect of sex, age at irradiation, ethnicity, dose-response and if possible, dose fractionation will be evaluated as well as interactions among these factors.

Populations receiving diagnostic irradiation are described below.

14. A cohort analysis is being conducted in a population of more than 32,000 twins born in Connecticut from 1930-1969 and followed to age 15 to evaluate cancer risk from prenatal x-ray exposure. Twins were chosen for study because the likelihood of medical selection bias would be reduced, i.e., most mothers were x-rayed because of a suspected twin pregnancy or to determine fetal positioning prior to delivery and not for any medical condition that could predispose to childhood cancer. An evaluation of prenatal x-ray exposure as a factor in childhood cancer has continued in Sweden. This research is based on a nationwide registry of more than 100,000 twins born between 1926-1967, among whom about 100 cases of verified childhood cancer have been found. Two twin controls have been selected for each case. Prenatal and early postnatal x-ray exposures have been determined through searches of hospital and prenatal clinic records.

15. Patients who received multiple chest fluoroscopies during pneumothorax treatment of tuberculosis between 1930 and 1954 are being followed to identify the anatomic sites with increased cancer risks. Attempts are being made to quantify these risks and to describe the duration of latency periods, changes of risk with time after treatment, age of the subject at the start of treatment, and age at the time of observation. Cancers of the breast, lung, esophagus and thyroid are of particular interest. Studies are being conducted in Massachusetts, Connecticut, and Denmark to clarify further the carcinogenic effect of multiple low-dose x-ray exposures in both men and women.

16. Using the resources of prepaid health plans in Oakland and Los Angeles, California and Portland, Oregon, 1,256 cases of leukemia and lymphoma and 1,578 controls have been identified. Long-term histories of diagnostic x-ray exposures have been obtained for all subjects. The possible association of leukemia and lymphoma with radiation dose to active bone marrow is being evaluated. Analyses have been completed.

17. A feasibility study of 1,645 patients treated for scoliosis at four Minneapolis-St. Paul, Minnesota hospitals from 1935-1965 was completed. These patients received a large number of full spinal anterioposterior x-ray examinations during a 3- to 5-year period in adolescence to monitor the progression of spinal curvature and treatment effects. The average patient received 43 spinal x-rays. The doses to the developing breast tissue in young girls were estimated to average 12 rad and may have been substantial enough to increase their risk of breast cancer.

18. A feasibility study of cancer risk in children who received multiple chest fluoroscopies during cardiac catheterization was completed at four hospitals which were at the forefront of cardiac catheterization in the early 1950s. This study evaluated the adequacy of exposure data and length of follow-up time. Rosters of patients will be compiled for possible study in the future. Subsequent risk of leukemia, breast cancer, and thyroid cancer would be evaluated. Additional feasibility work is being conducted in England and Holland to learn whether a sufficiently large sample might be available for study.

19. Analysis of a study of childhood cancer in relation to prenatal irradiation has continued. Childhood cancer deaths in the period 1960-69 among children who had been born in military hospitals were identified in a study conducted by the Medical Follow-up Agency, National Academy of Sciences. Two control births for each child were chosen from the same hospital of birth, born as near in time to the day of birth of the case as possible. The virtues of this study design were that (a) information concerning radiation exposures would be available in the hospital records; there would be no need to rely on statements of uncertain reliability made years later by parents; (b) information about the parents would also be available in the records--data related to social class, such as military rank and education, history of previous pregnancies and their outcomes, parental ages, etc.; and (c) the decision to do pelvimetry or other radiological procedures would, in a military hospital, not be influenced by economic constraints, i.e. ability to pay for the procedures.

Populations receiving isotopes are described below.

20. A study to evaluate the carcinogenic risks associated with diagnostic and therapeutic exposures to radioactive iodine in Sweden is continuing. Approximately 60,000 patients are being studied. A second follow-up of patients originally identified in the National Cooperative Thyrotoxicosis Therapy Follow-up Study (TT Study) is also continuing. Morbidity and mortality data are being collected on 23,000 persons treated by radioactive iodine, 131-I, for hyperthyroidism and 14,000 patients treated for hyperthyroidism by either surgery or anti-thyroid drugs. Radioactive iodine is an important isotope used in medicine, a major component of fallout from nuclear weapons tests, and also a major release product from nuclear power reactors. There is considerable controversy over the effectiveness of radioactive iodine in inducing malignancies, and further studies in this area are warranted. In this regard, a feasibility study was initiated in Israel to learn whether it would be valuable to investigate the late effects following diagnostic iodine given to approximately 30,000 persons.

21. A clinical evaluation of persons with nodular thyroid disease is continuing in collaboration with Brookhaven National Laboratory (BNL). These patients were initially identified in the TT Study and received 131-I therapy for hyperthyroidism. They developed palpable thyroid nodules one or more years after 131-I treatment. These nodules, however, were not clinically evaluated by the end of the study. BNL, in collaboration with clinicians who originally participated in the TT Study, will locate these patients and invite them to return to the clinic for an examination of the thyroid gland. The final clinical diagnosis will be analyzed as a function of 131-I dose, type of hyperthyroidism, age at first treatment, and duration of follow-up to assess the risk of thyroid disease following 131-I therapy.

22. The time course and dose dependence of the incidence of bone-sarcomas among 900 German patients treated with high doses of radium-224 have been anlayzed in terms of a proportional hazards model with a log-normal dependence of time to tumor and a linear-quadratic dose relationship.

Other projects are intended to strengthen inferences from studies of medically irradiated populations in general.

23. Dosimetry: An essential part of the program of epidemiologic studies of medically-irradiated populations is accurate dosimetry for specific organs. A team of medical physicists has been formed to work with the Branch on dosimetry problems using physical measurements on patients, anthropomorphic phantoms, and a Monte Carlo computer code developed in collaboration with the Oak Ridge National Laboratory and the Center for Devices and Radiological Health, Food and Drug Administration. Radiation dose estimates for specific organs have been obtained for tuberculosis patients repeatedly exposed to fluoroscopic x-rays, cervical cancer patients treated with intracavity radium and external beam x-rays or gamma rays, children irradiated for enlarged tonsils, children irradiated for tinea capitis, persons with leukemia and lymphoma who received diagnostic x-rays, persons exposed to multiple diagnostic x-rays for monitoring the progression of scoliosis, patients treated with neutrons for cancer, children treated with radiotherapy for cancer who subsequently developed a second malignancy, and women treated with radiation for breast cancer who subsequently developed a second breast cancer. Determinations are ongoing for women irradiated for breast cancer, benign gynecological disorders, infertility, or endometrial cancer who subsequently developed leukemia; and persons irradiated for treatment of peptic ulcer.

24. Biochemical and cytogenetic studies: The value of cytogenetic aberration data as a biological dosimeter in persons with partial-body irradiation is being explored in five medically-irradiated populations in collaboration with cytogeneticists at Oak Ridge Associated Universities. The objectives are: to evaluate chromosome aberrations as biological dosimeters for partial-body radiation exposure; to contrast the dose-response relationships of the frequency of aberrations per unit dose with similar dose-response data on cancer risk in the same irradiated populations; and to investigate the influence of age, sex, fractionation of dose, duration of time since exposures, and total dose on the yield of chromosome aberrations, through comparable analyses of different data sets. Populations being evaluated include persons irradiated for enlarged tonsils as children, cervical cancer patients, tuberculosis patients, persons exposed as infants for enlarged tonsils or thymic glands, and women irradiated for benign gynecologic disease. Chromosome aberrations are also being analyzed in women residing in areas of high and normal background levels of natural radiation in China. Among persons irradiated for enlarged tonsils, serum tests include measurements of thyroglobulin concentrations including T3, T4, TBGI, calcium, TSH, and AMA.

    Cultured skin fibroblasts from several irradiated populations are being obtained to evaluate the possibility that abnormal in vitro sensitivity to ionizing radiation, indicating perhaps an impaired ability to repair damaged DNA, might be associated with an enhanced risk of radiogenic cancer. To evaluate an unusual lowering of breast cancer risk following ovarian or adrenal irradiation for cervical cancer among premenopausal and postmenopausal women, serum determinations of hormones (estrone, estradiol, testosterone, and androstenedione) are being made. Currently, serum

samples have been collected from over 350 cervical cancer patients who were treated an average of 20 years ago and have been followed as part of the international radiation study of cervical cancer patients. In addition, serum samples are being collected from women treated more recently (2, 5, 10 or 15 years post-treatment), as well as pre-treatment and 6-month post-treatment samples from newly diagnosed cervical cancer patients. Fifteen women who received radiotherapy and 10 women who received surgery will be evaluated for each interval group.

B. Atomic Bomb Survivors. Beginning in 1979, a program of collaborative epidemiological studies was initiated between the Radiation Epidemiology Branch (REB) and the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan. Through the Japanese family registry system, RERF obtains virtually complete mortality follow-up on a defined sample of 94,000 atomic bomb survivors and another 26,000 nonexposed residents of the two cities. This body of data is undoubtedly the most important single source of information on cancer risk in human populations following exposure to ionizing radiation. A dosimetry system, providing individual radiation dose estimates for the great majority of the exposed sample members, has recently undergone a major revision. In collaboration with the local medical societies, RERF manages community-based tumor and tissue registries and a leukemia registry covering the two cities. Other important resources are a clinical subsample, originally of size 20,000, on which biennial medical examinations have been performed since 1958 and for which there are extensive clinical records and biological specimens such as stored serum samples, and active programs in laboratory medicine, cytogenetics, biochemical genetics, and molecular biology. An autopsy program has resulted in an extensive collection of tissue specimens. RERF has a modern computer system, and substantial improvements have been made in recent years to improve accessibility to the extensive data base resulting from past and current studies.

Through its collaborative program with RERF, the REB seeks to clarify the risk of cancer following radiation exposure, using several different approaches:

1. Site-specific studies of cancer incidence in the mortality sample, as ascertained from a thorough survey of all locally available sources, including death certificates, tumor and tissue registries, autopsy files, and hospital and clinic records. Currently, major emphasis is being placed on such studies and new initiatives are planned with respect to the breast, lung, and thyroid. Two particularly hopeful developments are the increased interest among local pathologists in improving completeness of cancer ascertainment at the incidence level and the apparent availability of information on incident cases diagnosed outside the Hiroshima and Nagasaki reporting areas, from regional and national tumor registries. Senior investigators from RERF and the REB jointly prepared a platform protocol for incidence studies, which lay out basic principles of study design and analysis, and arrangements for enlisting the collaboration of individual pathologists who would assume primary responsibility for case acquisition and review. This protocol was reviewed recently by RERF and its Board of Scientific Counselors and by the local pathology associations of Hiroshima and Nagasaki, and accepted as the basis for future studies of this type.

2. Case-control interview studies of other risk factors for cancer sites already studied at the level of incidence; these other factors are of interest as possible causes in themselves and as possible modifiers of the influence of radiation dose. Currently, colon and rectal cancer are being investigated for associations with diet, occupation, and physical activity, while diet and reproductive history are the focus of a new study of thyroid cancer. Current studies of breast and lung cancer will be expanded to include cases diagnosed within the past 5 years or so.

3. Reviews of histological materials, from the A-bomb survivors and from other exposed populations, by binational panels of pathologists to establish diagnoses, investigate possible relationships between histological type and radiation dose or other factors, or to clarify observed epidemiological differences. An ongoing study compares high-dose and low-dose lung cancer cases, matched by smoking history, among A-bomb survivors and Colorado uranium miners, in the hope of clarifying apparent epidemiological differences between these two populations in terms of lung cancer risk in relation to radiation dose and smoking. A total of 300 cases was reviewed in two sessions in Grand Junction, Colorado, and Hiroshima. Reviews were also conducted in two stages, a blind review by individual pathologists, and a consensus review using television and multiheaded microscopes.

4. Pathology reviews of tissue obtained at autopsy from subjects without clinical evidence of cancer, for the purpose of finding dysplastic lesions possibly related to radiation dose or other risk factors. Current studies of this type are concerned with breast tissue obtained at autopsy from women without clinical breast cancer and with esophageal tissue from persons without clinical esophageal cancer, but with quantified exposures to radiation and alcohol.

5. Laboratory assays of stored serum samples, obtained well before cancer diagnosis, from cancer cases and controls in search of possible indicators of cancer risk or conceivably of sensitivity to radiation carcinogenesis. Current investigations involve hormonal analyses of breast, endometrium, thyroid, and prostate cancer cases and controls, and nutrient assays of lung and stomach cancer cases and controls.

C. Occupational and Environmental Exposures. The objectives of this project area are to evaluate the long-term effects of chronic exposure to radiation as a consequence of occupational or environmental exposures and to collaborate with other governmental agencies involved in radiation research. Although the possibility of increased cancer risk associated with chronic occupational exposure to low-linear energy transfer radiation is of concern both for public health and radiation standard-setting, the only valuable quantitative information available to estimate this risk is derived from populations with acute and largely high-dose exposures. These estimates are subject to uncertainties associated with the assumed shape of the dose-response function used for downward extrapolation of risk.

1. The existence, since 1926, of a professional registry of about 175,000 medical x-ray technologists offered a unique opportunity for studying a large and well-defined population occupationally exposed to highly

fractionated low-LET radiation. Since most x-ray technologists are women, the registry provides a chance to study the two most sensitive organ sites for radiation carcinogenesis in women, the breast and the thyroid, at the level of incidence in a population with at least some exposure at particularly vulnerable ages. Questionnaires have been sent to approximately 165,000 active and inactive members, with nearly 90,000 returned to date. Additionally, 80% of the inactive members have been located. Various tracing strategies have been undertaken to locate the remaining inactive members and to encourage members who did not respond to the questionnaries to do so. This year an abbreviated telephone interview was added to the telephone prompting of nonrespondents to obtain information on cancer incidence.

2. In collaboration with the staff of the Baltimore Gas and Electric utility company, a cohort study of nuclear power workers at the Calvert Cliffs plant was conducted. Follow-up of the employees was completed, and lifetime occupational exposures estimated. Both the regular utility company workers and contractor employees were evaluated. Using the historical dose files of the Nuclear Regulatory Commission and the plant records, dose estimates could be obtained for 94 percent of the workers.

3. Radon exposure in the home has been suggested as an important risk factor for lung cancer. Scientific and technical collaboration has been undertaken with the New Jersey Department of Health in an investigation of 800 women with lung cancer and 800 matched controls to determine the extent of this risk. A Swedish study, similar to the one in New Jersey, is also underway. Pilot efforts have demonstrated the feasibility of obtaining alpha track detector evaluations of the residential radon exposures of these subjects and the reliability of this measurement method. The alpha track readings were found to be highly correlated with thermoluminescent detector measurements, although systematically they produced somewhat higher values. Alpha track exposure evaluations are now being extended to the rest of the study subjects. In all, 200 cases and 400 controls have been included. In China, a radon component has been added to a lung cancer case-control study in Shenyang. Approximately 400 women with lung cancer and 400 controls are having passive detectors placed in their residences. Collaboration on a radon study of lung cancer risk in Missouri has begun. A descriptive ecologic study of lung cancer mortality among persons living in counties encompassing the Reading Prong is continuing.

4. A study of thyroid nodules associated with high natural background areas in China has been conducted in Guangdong province. Over 2,000 women over the age of 50 years were examined for thyroid abnormalities by four U.S. physicians. Blood samples for thyroid hormone levels and for chromosome analysis have been obtained.

5. The possible health effects of electromagnetic radiation are the subject of much uncertainty and disagreement. The suggestion of effects in children is of particular interest. In this regard, and in collaboration with the Biostatistics Branch, a measurement protocol is being developed that might be appended to a nationwide case-control study of childhood leukemia.

6. Cancer incidence among 27,011 diagnostic x-ray workers was compared to that of 25,782 other medical specialists employed between 1950-1980 in China. The radiation workers included both radiologists and technicians. The comparison population consisted of 12,446 surgeons, 10,995 physicians, 2,306 otolaryngologists, and 35 other specialists working in the same hospitals during the same time period, but who did not use x-ray equipment in their work. Overall mortality and cancer incidence were determined through December 31, 1980.

7. Studies of mortality in the vicinity of nuclear installations in England suggest that risks of childhood leukemia may be increased in certain of those locations. To clarify this matter, a nationwide survey of mortality around nuclear reactors in the U.S. was initiated. All facilities that were ever operational and that exceed a nominal power output have been included. Mortality of counties with or near such nuclear installations will be compared over time with the mortality of counties without such facilities, but chosen for their similarity with the reactor counties on demographic and socioeconomic factors. Any differences found will be evaluated in detail in relation to the start-up date of reactor operation and other secular changes between the affected counties.

D. Methodologic Studies. This project area focuses on methods for increasing the information from existing bodies of data and for treating difficult analytic problems that arise during the course of other studies. In order to enhance the location capabilities to find persons exposed to radiation many years in the past, tracing methodologies are continually being developed and revised. The possibility of linking together state and national mortality files is being developed. To utilize the resources of cancer registries around the world, record linkage collaborations have continued. The usefulness of personal computers in epidemiologic research is being evaluated.

For cancer sites for which a wealth of epidemiologic data exists, attempts are made to resolve apparent inconsistencies among different studies and to strengthen inferences. This is accomplished by working in collaboration with the original investigators and by reanalyzing the basic data in parallel, using identical stratifications with respect to age at exposure, length of follow-up, and identical assumptions with respect to dose-response models and latent period. Such an approach is being taken with respect to thyroid cancer and breast cancer incidence data from several exposed populations. Special problems of estimating cancer risk from low-dose exposures to ionizing radiation have been explored, including statistical power, sample size, and dose-response model assumptions. Bayesian models have been considered for incorporating information from experimental radiobiology. The proportional hazards method was adapted to a factorially designed, long-term, animal experiment to assess possible interactions between radiation and other carcinogens in the induction of mammary tumors. Breast cancer risk among A-bomb survivors has been explored using new models in which the temporal distribution of baseline and excess risk are compared, as well as integrated risk over the entire period of observation. Analysis of the potential risks of lung cancer associated with indoor radon gas has been conducted. New statistical methods were developed to analyze interaction between radiation and other risk factors in a case-control study of breast cancer in which cases and controls were matched on radiation dose.

E. Consultant Activities and Services on Expert Committees. Branch members have served as consultants or committee members for the National Council on Radiation Protection and Measurements, the Department of Energy, the Department of Defense, the Oak Ridge Associated Universities, the Environmental Protection Agency, the DHHS Subcommittee to Coordinate Federal Radiation Activities, the National Aeronautics and Space Administration, the International Commission on Radiation Protection, the World Health Organization, and the National Academy of Sciences' Committee on the Biological Effects of Ionizing Radiations (BEIR V).

F. Review Papers. Several review papers concerning health effects following exposure to ionizing radiation were written, including a review of cancer following medical irradiation, the possible risk of second primary cancers associated with irradiation in breast-conserving therapy, the risk of lung cancer associated with radon, the potential risks of low-level radiation wastes, the statistical aspects of estimating cancer risks from low doses of ionizing radiation, the importance of latent period, the importance of risk projection and time-response models, and the long-term effects of radiation upon children.

G. Workshop. An International Workshop on Risks from Radium and Thorotrast will be held in October 1988. This workshop is jointly sponsored by the National Cancer Institute, the Department of Energy and the Commission of the European Communities. A major objective is to understand the mechanisms and evaluate the risk coefficients for cancers induced by internally deposited alpha-particle emitters in German patients injected with 224-radium, the U.S. and British radium dial painters, and patients injected with thorotrast.

A workshop on thyroid cancer in China was held in July 1988. The purpose was to discuss in detail the results from our collaborative study of thyroid neoplasms among women in China living in areas of high and normal natural background radiation. The enhanced radiation is the result of naturally occurring monazite sands which have a high content of radioactive thorium.

Major Findings:

A. Medical Exposures.

1. The international study of 200,000 cervical cancer patients treated with radiation and/or surgery suggests that the pattern of leukemia incidence associated with different levels of radiation dose is consistent with a model postulating increasing risk with increasing exposure, modified at high doses by increased frequency of cell death. The risk estimate of 1% increased relative risk (RR) per rad for leukemia is consistent with other studies and was estimated from a model including a negative exponential cell-killing term and a linear induction term. New cancers linked to radiation included cancers of the rectum and vagina. Very high doses, on the order of several thousand rad, were also found to increase the risk of cancer of the bladder and possibly uterine corpus, bone and non-Hodgkin's lymphoma. Doses on the order of several hundred rad increased the risk of stomach cancer and possibly kidney cancer, but not pancreatic cancer. Doses greater than 600 rad to the ovaries resulted in a 23% reduction in breast cancer risk. No overall risk was found for direct exposure to the

breast, despite an average dose of 31 rad; however, a weak suggestion of a dose response was apparent among women whose ovaries had been surgically removed. Radiation also was not found to increase the overall risk of cancers of the small intestine, colon, connective tissue, vulva, and Hodgkin's disease, multiple myeloma, and chronic lymphocytic leukemia. A twofold risk of radiogenic thyroid cancer, however, was suggested following an average dose of 10 rads.

2. A study of 13,385 tuberculosis patients treated between 1915-1954 in Massachusetts, many of whom received multiple chest fluoroscopies during pneumothorax treatment, indicates that repeated relatively low radiation doses pose a long-term risk of breast cancer, but not lung cancer or leukemia. An increased risk of thyroid nodules and esophageal cancer was also suggested.

3. Children irradiated for benign conditions of the head and neck were found to be at high risk of developing thyroid neoplasia in several studies. Radiotherapy for ringworm of the scalp also increased the risk of brain malignancies, and significant risks of leukemia and skin cancer were found for the first time. A study of children treated for enlarged tonsils, including physical examinations of exposed and nonexposed persons, suggests an increase of radiogenic thyroid nodules. However, contrasting findings from questionnaire studies with those from physical examinations suggest that radiogenic thyroid cancer may have been overestimated in previous surveys because of extreme underascertainment of thyroid tumors in nonexposed populations.

4. The development of cancers of the bone appeared to be associated with radiation therapy for childhood cancer, and a dose-response over a wide range of doses was observed.

5. Studies of cervical cancer patients found a significant dose-dependency with increasing bone marrow dose for stable but not for unstable chromosome aberrations. Increased aberrations were detected up to 35 years after exposure, indicating that radiation damage can persist for extremely long periods of time. The percentage of aberrant cells among cervical cancer patients was only 3%, in contrast to 9% found among atomic bomb survivors, despite the much higher average doses received during radiotherapy. These data support the notion that high doses to small volumes of tissue result in cell death or inviability that must deplete the pool of cells available for aberration evaluation. When adjustment was made for cell-killing effects within the high dose pelvic area, the chromosome aberration frequencies and percent aberrations per unit dose overlapped for cervical cancer patients and atomic bomb survivors. These data thus provide additional confirmation that the very low risk of leukemia in cervical cancer and other patients' given localized high-dose radiotherapy is the result of cell-killing effects of radiation.

6. A population-based case-control study of thyroid cancer in Connecticut indicated a high risk associated with radiotherapy for benign head and neck diseases when exposure occurred under age 10. No risk was found among persons diagnosed with thyroid cancer under age 35 in 1978, a finding

consistent with the declining use of radiotherapy for benign conditions in the 1950s. About 9% of the thyroid cancers could be attributed to prior childhood head and neck irradiation. Pregnancy after irradiation appeared to potentiate the risk of thyroid cancer.

7. A significant reduction in the risk of childhood cancer among 32,000 twins born in Connecticut was found in a record-linkage study when cancer rates in the general population, mainly singletons, were used for comparison. The deficit was concentrated among male twins. The reasons why twins are apparently at lower risk for cancer development than singletons are not clear.

8. The results of a feasibility study of cancer morbidity and mortality among 1,030 scoliosis patients indicated a nearly twofold excess of breast cancer compared to the general population (11 observed, 6 expected). The risk of breast cancer increased directly with increasing length of time since exposure, increasing number of x-ray films, and increasing radiation absorbed dose to the breast. Based on these findings, the study was expanded to include approximately 7,000 women with scoliosis.

9. The prevalence of thyroid, parathyroid, and salivary abnormalities was determined in 91 women who received an average of 112 fluoroscopic chest examinations during pneumothorax treatment for tuberculosis more than 40 years ago, compared to 72 women treated by other modalities. An excess of thyroid nodules and autoimmune thyroid disease was observed among the exposed women. The study suggests that susceptibility of the thyroid to low-dose radiation is present even when the dose is protracted over years and that low-dose x-ray exposure of the thyroid gland may predispose to autoimmune thyroid disease.

10. A population-based study of women irradiated for Hodgkin's disease found a fourfold risk of developing breast cancer 10 or more years after initial treatment. Eight of the 9 breast cancers developed in women irradiated at ages under 40, including 4 women exposed in their teens. These results suggest that women receiving radiotherapy for Hodgkin's disease at a young age should be carefully monitored for late occurring subsequent breast cancer.

11. A population-based case-control study in Connecticut found that there was little evidence that radiotherapy for breast cancer increased the risk of leukemia. Local radiation doses to each of 14 bone marrow components for each patient were reconstructed; the dose averaged over the entire body was 530 rad (5.3 gray). There was no indication that risk varied over categories of radiation dose. These data exclude an association between leukemia and radiotherapy for breast cancer of 2.2-fold with 90% confidence, and provide further evidence that cell death predominates over cell transformation when high radiation doses are delivered to limited volumes of tissue.

12. A diagnostic x-ray study was conducted within two prepaid health plans. Over 30,000 x-ray procedures were abstracted from hospital records and categorized, eliminating the possibility of response bias associated with

interview studies. No association was found for chronic lymphocytic leukemia. For all other forms of leukemia combined, there was a significant increase in risk with increasing number of x-rays; however, this trend progressively diminished when x-rays near the time of diagnosis were excluded. The findings for non-Hodgkin's disease were similar. These data suggest that x-rays might not be causal factors but simply related to conditions that portend the development of leukemia or lymphoma.

B. Atomic Bomb Survivors.

1. A recent survey of breast cancer incidence found a dose-related excess among women who were under age 10 at the time of the bombings (ATB), comparable to that seen among those who were teenagers ATB, while there was no evidence of excess risk among those exposed after age 40 ATB. As was seen for the older cohorts ATB, the excess risk did not appear until ages at which breast cancer risk normally becomes appreciable. Excess risk was roughly proportional to dose; the additional number of cases provided direct evidence of an excess risk at breast tissue doses in the 8-16 rad range. A preliminary analysis of data from a current survey of colorectal cancer incidence has found a dose response for colon cancer, but no increased rectal cancer risk.

2. The findings from a recent case-control study of lung cancer suggest an additive, rather than multiplicative, relationship between radiation dose and cigarette smoking. Due to the important implications of this finding for risk estimation, an extension of the study, using more recent cases, is planned. Data from this study also indicate an enhanced lung cancer risk among nonsmoking wives of male smokers. Preliminary findings from another case-control interview study indicate that many reproductive factors related to breast cancer risk among Japanese women interact multiplicatively (synergistically) with radiation dose, while an additive relationship can be rejected. A lengthy lactation history appears to be strongly protective against breast cancer and against radiation-induced breast cancer, in particular, in this population. Preliminary findings from a current study of colorectal cancer indicate a lower risk of colon cancer among subjects whose normal occupation involved significant physical exercise. Breast cancer cases were more likely to have been exposed before their first pregnancy then age and dose-matched controls. This relationship holds even after adjustment for age at first delivery, and indicates a greater sensitivity to radiation-induced cancer at that reproductive stage.

3. Preliminary findings from a current histopathological study of breast tissue indicates a dose-related increase in dysplasia that parallels the findings for breast cancer incidence; in particular, the dose-related dysplasia increase is less extreme among women exposed at older ages. Senior investigators from RERF and this Branch jointly prepared a platform protocol for incidence studies, laying out basic principles of study design and analysis, and institutional arrangements for enlisting the collaboration of individual pathologists from local institutions who would assume primary responsibility for case acquisition and review. This platform protocol has been reviewed by RERF, the RERF Board of Scientific

and has been accepted by them as the basis for future incidence studies. The first new study to be undertaken according to these guidelines was begun in May 1988, and covers breast cancer incidence during 1950-1985.

4. Papers have been written comparing the effect of the new dosimetry changes on risk estimates among the survivors of the atomic bomb. In terms of total kerma (essentially whole-body gamma plus neutron exposure), risk estimates are 75-87% higher with the new dosimetry. At an assumed constant relative biological effectiveness of 10 for neutrons, the effect of the dosimetry revision is to increase organ dose risk estimates, relative to those based on the old dosimetry, by 30% for nonleukemia and 80% for leukemia. The city difference in dose is no longer statistically significant. There is substantial question of the linearity in dose-response, in the sense of a leveling off at higher doses.

C. Occupational and Environmental Exposures.

1. Preliminary analysis of thyroid cancer risk among 80,000 x-ray technologists who responded to a mail questionnaire indicates a twofold risk compared to population expectation.

2. X-ray workers in China had a 50% higher risk of developing cancer than other specialists not frequently exposed to radiation during employment. Cancers linked to radiation work included leukemia, breast and thyroid, and possibly bone and skin. High risks of cancers of the esophagus and liver were not consistent with a radiation effect and might reflect differences between groups of hospital workers in social class, alcohol intake, dietary habits, and other risk factors. No excess lung cancer or multiple myeloma was observed. The excess leukemia followed a wave-like pattern, peaking 10-14 years after start of employment and decreasing to normal levels after 20 years.

3. The risk of radon-induced lung cancer among residents of single family homes in the U.S. was estimated using models recently developed by the National Academy of Sciences BEIR IV Committee. These models predict that approximately 14% of lung cancer deaths (about 12,700 deaths per year) may be due to indoor radon exposure. The attributable risks due to radon are similar for males and females and for smokers and nonsmokers, but higher baseline risks of lung cancer result in much larger numbers of radon-attributable cancers among males (approximately 9,500) and among smokers (approximately 11,000). Most of the contribution to the attributable risks arises from exposure rates below 4 pCi/l. As a result, if all exposure rates which exceed 4 pCi/l (approximately 8% of homes) were eliminated, the models predict that the annual lung cancer burden would drop by 4%, or by about 3,600 lung cancer deaths, in contrast to a maximum reduction of 14% if all indoor radon exposure was eliminated.

4. No risk of radiogenic thyroid tumors was found among 2,000 women in China who underwent physical examinations. Half of the women resided in areas of enhanced natural background radiation due to monazite sands. The average thyroid dose was estimated to be between 8 and 18 rad.

D. Methodologic Studies.

1. A case-control interview study of breast cancer among A-bomb survivors required the development of a new method for estimating interaction between radiation dose and other risk factors because matching was done with respect to dose. The method is more powerful than conventional analyses in which matching does not depend on dose.

2. A review of hypothesis testing and confidence interval estimation procedures for lognormal distribution parameters outlined methods useful for the estimation of radiation doses from radioactive fallout. Interactive computer programs were developed which greatly increase the usability of these procedures.

3. X-rays were found to interact in an additive manner with several mammary carcinogens in the female Sprague-Dawley rat.

4. Development and documentation of AMFIT (a program for the analysis of grouped survival data using Poisson regression methods) and PYTAB (a production of complex person-year tabulations) have continued. Versions of these programs will be included as part of the REB-developed package of epidemiological programs for personal computers. These programs were used by the National Academy of Sciences' BEIR IV committee in their analyses of the risks associated with radon exposure and they are currently being used by the BEIR V committee as the primary tools for the analysis of data from a wide variety of studies of radiation effects.

5. Preliminary copies of "Epitome: Epidemiologic Analysis with a Personal Computer" have been distributed in a limited fashion. This REB-developed package of epidemiologic programs should be completed within the year.

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CONTRACTS IN SUPPORT OF THIS PROJECT

ENERGY, DEPARTMENT OF (Y01-CP-10504)

Title: Studies on Radiation-Induced Chromosome Damage in Humans

Current Annual Level: $149,000

Person Years: 2.8

Objectives: To study radiation-induced chromosome damage in five different human populations, irradiated from 15 to 50 years ago. All five populations received partial-body exposures from diagnostic or therapeutic radiation. The project was undertaken to determine the type and frequency of chromosome aberrations in circulating lymphocytes and to compare dose-response curves among these five populations with respect to dose, quality of radiation, fractionation, age, and sex. The purpose is (1) to evaluate the usefulness of chromosome aberration frequency as a biological dosimeter for partial-body exposures, (2) to contrast the dose-response relationship of the frequency of aberrations per unit dose with similar dose-response data on cancer risk in the same irradiated populations, and (3) to obtain insights into a biological effect that may be similar to radiation carcinogenesis.

Methods Employed: Chromosomal aberrations are being determined and analyzed in 900 subjects selected from among five populations exposed to partial-body diagnostic and therapeutic radiation during the period 1930-1970, which are currently under study by the Branch for late health effects in relation to individual dosimetry. These populations are cervical cancer patients given radiotherapy, tuberculosis patients given multiple chest fluoroscopies, persons irradiated for lymphoid hyperplasia during childhood, persons irradiated for enlarged thymus glands during infancy, and women irradiated for benign gynecologic disorders. About 50 nonexposed persons from each of these populations are selected as controls. Blood specimens, drawn at the hospitals where these persons were treated, are analyzed at the DOE-supported radiation cytogenetic laboratory at the Oak Ridge Associated Universities and the Laboratory of Cytogenetics at Roswell Park Memorial Institute, Buffalo, New York.

Major Contributions: To date, cultured blood samples (200 cells each) have been completed on 159 tonsil patients, 287 cervical cancer patients, 150 tuberculosis patients, 202 patients treated as children for enlarged thymus glands and 60 women irradiated for benign gynecologic disorders. Further analyses now indicate a small, but statistically significant, difference in the frequency of chromosome aberrations in exposed persons as compared with nonexposed persons treated during childhood for enlarged tonsils. Age, sex, and smoking histories were controlled in the analysis. Studies of cervical cancer patients found a significant dose-dependency with increasing bone marrow dose for stable but not for unstable chromosome aberrations. Increased aberrations were detected up to 35 years after exposure, indicating that radiation damage can persist for

extremely long periods of time. The percentage of aberrant cells among cervical cancer patients was only 3%, in contrast to 9% found among atomic bomb survivors, despite the much higher average doses received during radiotherapy. These data support the notion that high doses to small volumes of tissue result in cell death or inviability that must deplete the pool of cells available for aberration evaluation. When adjustment was made for cell-killing effects within the high dose pelvic area, the chromosome aberration frequencies and percent aberrations per unit dose overlapped for cervical cancer patients and atomic bomb survivors. These data thus provide additional confirmation that the very low risk of leukemia in cervical cancer and other patients given localized high-dose radiotherapy is the result of cell-killing effects of radiation.

TEXAS, UNIVERSITY OF, M.D. ANDERSON HOSPITAL (NO1-CP-01047)

Title: Studies of Iatrogenic Cancer and Radiation Dosimetry

Current Annual Level: $220,000

Person Years: 2.0

Objectives: To provide radiation dosimetry necessary to estimate organ doses received during exposure to either therapeutic or diagnostic radiation.

Methods Employed: Physics measurements are being made for x-ray machines and intracavitary isotopes. These include orthovoltage, betatron, megavoltage x-ray machines, Van de Graaff machines, and cobalt-60 units, in addition to radium and cesium intracavitary sources. Abstracted dosimetry data from all collaborating centers are further evaluated and organ-specific doses estimated, either by measurement, computer simulation, or literature review.

Major Contributions: The contractor has developed and refined a measurement program to obtain organ-specific doses following treatment for cervical cancer. Calculations of active bone marrow dose and measurements have been performed and compared with the results from a Monte Carlo computer technique for a mathematically described anthropomorphic phantom. Organ doses for 15,000 cervical cancer patients have been determined. Organ dosimetry has also been provided for (1) studies of cancer following childhood cancer treatment with radiation, (2) leukemia and lymphoma following diagnostic x-ray procedures, (3) cancer following treatment for testicular cancer, (4) contralateral breast cancer following radiotherapy for an initial breast tumor, (5) cancer following radiotherapy for benign gynecologic disorders, (6) patients undergoing computerized axial tomography (CAT) scans, (7) patients undergoing multiple x-rays for scoliosis, (8) leukemia following radiotherapy for breast cancer, (9) thyroid cancer following irradiation for enlarged tonsils, (10) cancer following radiotherapy for tinea capitis, (11) patients undergoing heart catheterization, (12) cancer following radiotherapy for retinoblastoma, (13) cancer following irradiation for peptic ulcer, (14) women irradiated for benign gynecologic disorders, (15) women irradiated for infertility, and (16) leukemia following radiotherapy for endometrial cancer.

WESTAT, INC. (NO1-CP-31035)

Title: Support Services for Radiation and Related Studies

Current Annual Level: $1,582,395

Person Years: 11.0

Objectives: To obtain technical (nonprofessional), managerial, and clerical support for epidemiologic studies. The contractor functions in a supportive role carrying out specific tasks and does not engage in independent research.

Methods Employed: All phases of support services are being supplied, including: (1) preparing data collection forms; (2) preparing manuals for abstracting, coding, interviewing, and tracing; (3) tracing individuals to determine their vital status; (4) obtaining their consent to be interviewed; (5) interviewing or sending mail questionnaires; (6) obtaining death certificates; (7) abstracting, keying, editing, updating, and coding of data; (8) occasionally transporting biological specimens; (9) assessing exposure information; and (10) creating and manipulating data files.

Major Contributions: The contractor has provided support services for the following studies: (1) the follow-up study of cervical cancer patients treated in U.S. clinics; (2) case-control studies within U.S. cancer registries for the cervical cancer study; (3) questionnaire preparation and tracing for the x-ray technologist study; (4) leukemia case-control study among breast cancer patients reported to selected SEER cancer registries; (5) Veterans Administration adjuvant drug study evaluations; (6) clinical trial evaluations of leukemia risk following breast cancer; (7) follow-up and tracing for the TB-fluoroscopy breast cancer studies in Massachusetts and Connecticut; (8) study of cancer following radiotherapy for infertility in New York; (9) study of second breast cancer following radiation therapy in Connecticut; (10) case-control study of the risk of second malignancies following treatment for testis cancer; (11) cohort study of 3,000 children with lymphoid hyperplasia who were treated with and without radiation in Boston; (12) study of childhood cancer following prenatal x-ray in Connecticut and California; (13) feasibility study of nuclear power workers; (14) study of new cancers following treatment for retinoblastoma; (15) hormonal and chromosomal studies of cervical cancer patients; (16) feasibility study of thyroid abnormalities in high radiation background areas in China; (17) a feasibility study of cancer risk in children who underwent cardiac catheterization; (18) a study of radon exposure and lung cancer risk in New Jersey; (19) follow-up study of children irradiated for enlarged tonsils in Chicago; (20) study of leukemia following radiotherapy for uterine corpus cancer; (21) tracing support for studies of women receiving radiation treatments for benign gynecologic disorders; (22) questionnaire development for feasibility study of patients treated with neutrons; (23) tracing support for study of persons in Chicago irradiated for peptic ulcer; (24) mortality survey of persons living in counties near nuclear facilities; and (25) directing the management of all tracing activities of the Epidemiology and Biostatistics Program.

RESEARCH TRIANGLE INSTITUTE (N01-CP-31036)

Title: Support Services for Radiation and Related Studies

Current Annual Level: $383,812

Person Years: 3.2

Objectives: To obtain technical (nonprofessional), managerial, and clerical support for epidemiologic studies on populations exposed to ionizing radiation, with primary focus on persons with scoliosis who received multiple diagnostic x-ray exposures of the spine during adolescence and a nationwide follow-up study of patients treated for hyperthyroidism. The contractor functions in a supportive role carrying out specific tasks and does not engage in independent research.

Methods Employed: All phases of support services are being supplied, including: (1) preparing data collection instruments (medical abstract forms, questionnaires); (2) preparing training manuals for abstracting, coding, data editing, interviewing, and tracing; (3) tracing individuals to ascertain their vital status; (4) interviewing or sending mail questionnaires; (5) obtaining death certificates; (6) abstracting, coding, keying, editing, and updating of data; (7) assessing exposure information for purposes of radiation dosimetry; and (8) creating and manipulating data files.

Major Contributions: The major effort of this contract has been the support of a retrospective cohort study of cancer morbidity and mortality among scoliotics exposed to multiple diagnostic x-ray examinations during childhood and adolescence. The feasibility study was completed in December 1986. Although based on only 11 breast cancers occurring in some 1,000 women, this represented a nearly twofold excess. These results prompted the expansion of the study to include more centers so as to obtain a large enough sample to address this issue adequately.

Extensive support has also been provided to the study of hyperthyroid patients: (1) the preparation of data tapes for record-linkage with the National Death Index and the Health Care Financing Administration (HCFA), and (2) assisting with patient identification efforts. The following tasks have been completed: (1) the identification of original patient rosters; (2) submissions have been made to HCFA, the National Death Index, and various state mortality tapes to identify deceased patients; (3) a 10% sample of deaths in the original follow-up study was selected (n=625), cause of death re-coded according to the rules of the International Classification of Diseases, 7th revision, and the re-code compared with the original code to determine the validity of nosology in the original study; (4) submissions have been made to credit bureaus, motor vehicle departments, and other tracing resources; and (5) death certificates are being obtained for identified decedents.

WESTAT, INC (NO1-CP-71107)

Title: Breast and Other Cancers Following X-Rays for Scoliosis

Current Annual Level: $478,598

Person Years: 4.1

Objectives. The main objective of this contract is to obtain managerial, technical, and clerical support for an expanded epidemiologic follow-up study of patients treated for scoliosis, which will be directed by the Radiation Epidemiology Branch, National Cancer Institute. The contractor will function in a supporting role, carrying out specific tasks, and will not engage in independent research.

Methods Employed: A cohort of approximately 7,500 additional women with scoliosis will be identified and cancer incidence and mortality will be determined from medical records, questionnaires, and death certificates. Contact has been made with the major clinics and orthopedic surgeons in the United States who have treated scoliosis patients for at least the past 30 years. It is anticipated that it will be necessary to pool populations from about eight different hospitals or clinics to obtain sufficient numbers. Clinicians from a number of states have indicated a willingness to participate, including ones in California, Massachusetts, Texas, Iowa, Missouri, Pennsylvania, Delaware, Georgia, and others. Demographic, medical and family history, x-ray exposure, and location information will be abstracted from the patient records. The number and types of x-ray films taken for each patient will be identified and tabulated. Radiation dose estimates will be developed under a different contract (NO1-CP-01047), based on information contained in the patient medical record and data from the x-ray films and machine parameters. Tracing of subjects will be conducted using resources of both the NCI and the support services contractor. It is estimated that about 35% of the tracing will be conducted through NCI resources and 65% through the contractor resources. Once a person has been found, a questionnaire will be mailed to obtain information on medical history, family history of breast cancer, tumor diagnoses, nutritional factors, and reproductive factors (e.g., ages at first pregnancy, menarche, and menopause). Death certificates will be collected for all decedents. Reported cancers will be validated by obtaining hospital discharge summary, pathology, surgery, or autopsy reports.

Major Contributions: None to date. Contract recently awarded.

INFORMATION MANAGEMENT SERVICES, INC. (NO1-CP-61006)

Title: Biomedical Computing Support for the Radiation Epidemiology Branch

Current Annual Level: $337,911

Person Years: 5.0

Objectives: To obtain computer-related research and support services for the epidemiologic studies conducted by the Branch. The contractor functions in a supportive role, carrying out specific tasks, and does not engage in independent research.

Methods Employed: All phases of computer support are being supplied including: (1) coding, transcribing, and on-line and off-line data entry (keying); (2) developing computer programs, systems and documentation, as required; (3) using existing generalized software packages for statistical computation, retrieval, and report generation; and (4) maintaining and operating large data base systems.

Major Contributions: This contract has been in force since April 1986. The contractor has provided support for the following studies: (1) studies of multiple primary cancers; (2) cancer risk in x-ray technologists; (3) case-control study of breast cancer following diagnostic x-rays for tuberculosis; (4) software support for microcomputers; (5) noncentral T-distribution equations; (6) contralateral breast cancer study; (7) cancer risk in women irradiated for benign gynecologic disease; (8) cancer risk in tuberculosis patients; (9) cancer risk in scoliosis patients; (10) cervical cancer patient studies; (11) studies of radiation-induced thyroid neoplasms; (12) cancer following irradiation for tinea capitis; (13) chromosome damage following irradiation; (14) evaluation of Generalized Iterative Record Linkage Systems (GIRLS) from Canada; (15) case-control study of leukemia and preleukemia following radiotherapy and chemotherapy for breast cancer; and (16) cancer mortality among U.S. veterans in relation to smoking information obtained on questionnaires. On average, approximately 20 studies on projects are supported during any given month.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05368-05 REB

PERIOD COVERED

October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of Drug-Induced Cancer and Multiple Primary Cancers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. D. Boice, Jr.	Chief	REB	EBP	NCI
Others:	R. E. Curtis	Statistician	REB	EBP	NCI
	R. A. Kleinerman	Epidemiologist	REB	EBP	NCI
	M. A. Tucker	Clinical Investigator	EEB	EBP	NCI
	M. Blettner	Expert Statistician	REB	EBP	NCI
	E. Ron	Staff Fellow	REB	EBP	NCI

COOPERATING UNITS *(if any)*

Danish Cancer Registry (O. Jensen); M.D. Anderson Hospital (M. Stovall); Harvard Medical School (W. Moloney, H. Lisco); Tufts University (M. Kaplan)

LAB/BRANCH

Radiation Epidemiology Branch

SECTION

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	3.0	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to study the long-term health effects of drugs, especially therapeutic agents, as they may relate to carcinogenicity. In addition, the patterns of occurrence of multiple primary cancers are evaluated in terms of implications for etiologic research. Because many studies of radiation carcinogenesis involve the evaluation of second cancers following radiotherapy for a primary cancer, it is often convenient to evaluate, simultaneously, the effects of chemotherapeutic agents. Populations studied include patients treated in randomized clinical trials, patients reported to cancer registries in the United States and other countries, and patients treated at several large institutions. Additional details can be found in Project No. Z01CP04412-12 EEB, "Carcinogenic Effects of Therapeutic Drugs" and Project No. Z01CP04410-12 EEB, "Studies of Persons at High Risk of Cancer." In addition to the systematic study of therapeutic drugs, occasionally it is possible to evaluate other drug exposures in populations studied primarily for other reasons.

Alkylating agents to treat childhood cancer were associated with an increased risk of leukemia and bone cancer. Women with breast cancer who received chemotherapy are at an increased risk of leukemia. Commonly used drugs were not found to be related to thyroid cancer.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

John D. Boice, Jr.	Chief	REB	EBP	NCI
Rochelle E. Curtis	Statistician	REB	EBP	NCI
Ruth A. Kleinerman	Epidemiologist	REB	EBP	NCI
Maria Blettner	Expert Statistician	REB	EBP	NCI
Elaine Ron	Staff Fellow	REB	EBP	NCI
Margaret A. Tucker	Clinical Investigator	EEB	EBP	NCI
Robert N. Hoover	Chief	EEB	EBP	NCI
Joseph F. Fraumeni, Jr.	Associate Director		EBP	NCI

Objectives:

(1) To clarify the magnitude and determinants of risk of second cancers after chemotherapy. (2) To study the long-term effects of selected drugs in humans and to characterize risk in terms of dose and latent period as well as the influence of age, sex and race. (3) To evaluate the causes of multiple primary cancers.

Methods Employed:

1. A systematic evaluation of adjuvant drug therapy for cancer treatment has continued (see also, Project No. Z01CE04412-12 EEB, "Carcinogenic Effects of Therapeutic Drugs" and Project No. Z01CE04410-12 EEB, "Studies of Persons at High Risk of Cancer"). To evaluate the potential carcinogenic effects of various modalities in the treatment of cancer, information from several NCI-supported cancer treatment protocols is being combined and analyzed. The program of studies has been conducted in collaboration with the Division of Cancer Treatment. From a survey of NCI-funded protocols, a number of cancer treatment trials was selected for evaluation. Protocol chairmen and statisticians were contacted, available data evaluated, and abstract forms designed to obtain information on second cancers not readily available from computerized data. Collaboration has been obtained from the following surgical adjuvant groups: the Gynecologic Oncology Group, the Veterans Administration Surgical Oncology Group, the Eastern Cooperative Oncology Group, the Gastrointestinal Tumor Studies Group, the Brain Tumor Study Group, and the Southwest Oncology Group. Several large individual institutions (e.g., M. D. Anderson Hospital, Mayo Clinic, Roswell Park Memorial Institute, and Princess Margaret Hospital) have also collaborated in these studies. Drugs being evaluated include: methyl-CCNU ethyl-CCNU, cyclophosphamide, chlorambucil, 5-fluorouracil, nitrogen mustard, and others.

2. A case-control study of 220 children with second malignant neoplasms and 400 controls is currently under analysis to evaluate the relationship between therapy received for their first malignant neoplasm and the

development of their second neoplasm. These children were treated with a wide range of chemotherapeutic agents. Analyses for leukemia, bone cancer and thyroid cancer have been completed. Analyses for cancer of connective tissue are ongoing.

3. A population-based case-control study is being conducted to evaluate the risk of leukemia and preleukemia in breast cancer patients treated with chemotherapy. A feasibility study in Connecticut has been completed in which complete treatment details were abstracted from hospital and physician medical records for 20 cases and 60 matched controls. The study has been expanded to four additional cancer registries: Iowa, Detroit, Los Angeles, and Atlanta. Eighty-eight cases of leukemia and preleukemiafollowing breast cancer have been identified and 264 controls have been selected. Drug-specific risks will be quantified and compared, and the dose-response relationship for the most commonly used alkylating agents, melphalan and cyclophosphamide, will be estimated.

4. A case-control study in four U.S. cancer registries and in Denmark is being analyzed. Approximately 500 women who developed endometrial cancer as a second cancer following breast cancer therapy have been evaluated along with matched controls. Detailed information was collected on medical histories and estrogen exposures, allowing the risk of endometrial cancer to be evaluated in relation to estrogen use.

5. A case-control study was conducted in Copenhagen, Denmark to evaluate the interaction between estrogen use and obesity in the etiology of cancer of the corpus uteri. Altogether, 149 cases of histologically confirmed adenocarcinoma and 154 controls were evaluated.

6. The risk of commonly used drugs is being analyzed in a case-control study of 1,256 cases of leukemia and lymphoma and 1,578 matched controls using the resources of prepaid health plans in California and Oregon.

7. The risk of leukemia is being evaluated among patients treated with adjuvant chemotherapy during the conduct of two early clinical trials of breast cancer. Other cooperative groups in the United States, in particular the National Surgical Adjuvant Breast Project, have been contacted to extend these investigations.

8. Using the resources of the Veterans Administration clinical trials system, evaluation is ongoing of patients with colorectal cancer or lung cancer who received nitrogen mustard, cytoxan, methotrexate, or CCNU.

9. A mortality study of men and women treated with isoniazid for pulmonary tuberculosis in Connecticut and Massachusetts is continuing. Medical records and mail questionnaires were used to ascertain drug exposure.

10. A study is being conducted of epileptic patients who received phenobarbital, dilantin, and other anti-convulsive drugs to evaluate possible carcinogenicity, particularly in offspring exposed in utero. Cancer registry records in Denmark are being linked with hospital lists to ascertain cancers.

11. Risk factors for thyroid cancer were investigated in a population-based case-control study in Connecticut. Home interviews were conducted on 159 persons who developed thyroid cancer between 1978-1980 and on 285 controls. Detailed histories of commonly used drugs were taken.

12. The risk of second primary cancer was assessed among a cohort of 544 persons diagnosed with cutaneous T-cell lymphoma (mycosis fungoides and sezary syndrome) from the population-based Surveillance, Epidemiology, and End Results (SEER) cancer registries.

13. Radiation dose-response information is being obtained from studies of multiple primary cancers in cervical cancer patients treated in 16 oncologic clinics and 17 population-based tumor registries around the world.

14. A study was begun to identify patients treated with chemotherapy for a first cancer that may be at increased risk of a second primary cancer due to cytotoxic therapy. Data from the SEER cancer registries are currently being analyzed. Seventeen first primary sites (those commonly treated with chemotherapy) are being screened for increased risks of subsequent cancers, in particular excess solid tumors appearing 5 or more years after initial chemotherapy exposure.

Major Findings:

1. The risk of secondary bone cancer following childhood cancer therapy was found to be largely due to radiotherapy for the initial primary cancer, although an elevated risk from exposure to alkylating agents was also suggested.

2. The population-based case-control study of thyroid cancer did not find positive associations with the use of exogenous estrogens, lactation suppressants, oral contraceptives, alcohol, or most commonly used drugs. New associations, however, were suggested for prior history of benign thyroid nodules (RR=33), goiter (RR=5.6) and benign breast disease (RR=1.6), and for a family history of thyroid cancer (RR=5.2), vitamin D supplements (RR=1.8) and use of spironolatone (RR=4.3).

3 Preliminary results from a case-control study of Connecticut breast cancer patients showed an 11-fold increased risk of leukemia and preleukemia after alkylating agent therapy. The feasibility of obtaining treatment information on specific drugs in a population-based cancer registry study was demonstrated.

4. Among 12,000 patients known to have received chemotherapy for the treatment of breast cancer and reported to the SEER registries, a ninefold increased risk of acute nonlymphocytic leukemia was found. The increased risk first appeared two years after the breast cancer diagnosis, was highest in 5-year survivors, and was concentrated in patients with regional node involvement. Among women diagnosed with breast cancer

before the era of adjuvant chemotherapy (1973-1974), no excess leukemias were observed (RR=1.1).

5. New cancers linked to radiation following treatment for cervical cancer included the rectum (RR=1.8), vagina (RR=2.7) and possibly the cecum (RR=1.5).

6. Among women who have used menopausal estrogens, the risk of endometrial cancer was not increased with increasing obesity. Among non-users of estrogen, however, the risk of endometrial cancer rose with increasing degrees of obesity and reached fivefold for the most obese.

7. The frequently observed protective association of breast cancer with pelvic irradiation may be due, in part, to a decrease in estrone, testosterone or androstenedione--secondary perhaps, to adrenal irradiation.

8. A screening of 150,000 cancer patients treated with chemotherapy and reported to population-based cancer registries is being undertaken to identify possible increased risks of second cancers that may be due to their initial treatment. Preliminary findings suggest that acute leukemias are increased following chemotherapy for small cell lung cancer, breast cancer, ovarian cancer, testis cancer, Hodgkin's disease, non-Hodgkin's lymphoma, and multiple myeloma. Bladder cancer is elevated following chemotherapy for breast cancer, non-Hodgkin's lymphoma, and multiple myeloma. Lung cancers are in excess following non-Hodgkin's lymphomas and chronic lymphocytic leukemia. Patients receiving chemotherapy for ovarian cancer and chronic lymphocytic leukemia experience increased risks of subsequent colon cancer.

9. Among 544 patients with a first primary tumor reported as cutaneous T-cell lymphoma, a second cancer developed in 35 (6%), yielding a significantly elevated risk of 1.7. Excess second cancers of the lung may be due to their altered immune status and/or cancer therapies. The increased frequency of second colon cancer may provide a clue to common exposures or susceptibility mechanisms between these two sites.

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ANNUAL REPORT OF

THE EXTRAMURAL PROGRAMS BRANCH
EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1987 through September 30, 1988

The Extramural Programs Branch (1) plans, develops, directs and manages a national extramural program of basic and applied research in biometry, epidemiology, and related multidisciplinary activities; (2) establishes program priorities and evaluates program effectiveness; (3) provides a broad spectrum of information, advice and consultation to individual scientists and institutional science management officials concerning National Institutes of Health (NIH) and National Cancer Institute (NCI) funding and scientific review policies and procedures, preparation of grant applications and choice of funding instruments; (4) provides NCI management with recommendations as to funding needs, priorities and strategies for the support of relevant research areas consistent with the current state of development of individual research activities and the promise of new initiatives; (5) plans, develops and manages research resources necessary for the conduct of the coordinated research program; and (6) plans, organizes and conducts meetings and workshops to further program objectives, and maintains contact with the relevant scientific community to identify and evaluate new research trends relating to its program responsibilities.

Organizational Overview: The Extramural Programs Branch (EPB) is a component of the Epidemiology and Biostatistics Program and is responsible for grants, cooperative agreements, and extramural contracts focused on epidemiology and biostatistics. The Branch strives to promote multidisciplinary approaches to research in these areas. This symbiotic potential extends beyond the internal activities of EPB to the extramural community where interest in multidisciplinary efforts is increasingly evident. No rigid boundaries exist between the individual programs comprising the EPB. Indeed, as is evident from the program descriptions to follow, the activities of the Branch involve a high degree of integration and cooperative interaction between the respective program directors.

In 1985, in response to requests from members of the Division of Cancer Etiology (DCE) Board of Scientific Counselors, a workshop to explore ways to strengthen extramural epidemiologic research was held. Several recommendations emerged from the workshop which were presented to, and endorsed by, the Board of Scientific Counselors. Attempts have since been made by program staff to implement these recommendations. As a result, a Small Grants program for the epidemiology and biostatistics area has been created, with the first round of applications received during the 1986 fiscal year. Awards under this mechanism are intended to support initiatives which focus on 1) planning of a complex epidemiologic investigation, 2) developing or validating a laboratory procedure for the ultimate purpose of applying it to cancer epidemiologic research, or 3) carrying out an epidemiologic research project for which rapid funding is justified. The Small Grants program is an important innovation and the quality of applications continues to improve. Regarding other recommendations in the workshop report, etiology has been reinstated as an appropriate topic for preventive oncology grants, and our attempts to improve the PO1 guidelines to the benefit of epidemiologic investigators have been instrumental in the formulation of new guidelines, recently issued.

In general, the following discussion of program areas is restricted to research grants active in the period October 1, 1987 through May 15, 1988. Additional research grants will be funded during the remaining months of the fiscal year, but their individual focus and exact support level are uncertain at this time. We are able to estimate their impact on the budget at the Branch level, but not their impact on individual programs within the Branch.

Biometry and Genetic Epidemiology: Although this program is primarily composed of research grant activities, interagency agreements are also being utilized to determine the feasibility of linking existing data sources to provide epidemiologic resources to the extramural scientific community. A research contract has been implemented during this fiscal year which is exploring the feasibility of extending the coverage of the National Death Index for years prior to 1979. This program area includes a wide variety of research activities, including mathematical models; statistical techniques for evaluating the effects of potential carcinogens; effects of patient characteristics on morbidity or mortality risks; record linkage for investigations involving special population groups, cancer registries or death lists; relation of cancer susceptibility to cytogenetics and somatic cell genetics; and the design of statistical techniques to optimize cancer screening tests.

Epidemiology: This program area is primarily composed of research grant activities and, in addition to its other functions, administers the epidemiology Small Grants program. Research areas of interest include investigations focusing on the natural history of neoplasia in humans; the incidence and prevalence of various human cancers as a function of geographic location; etiologic risk factors (both intrinsic and extrinsic) related to human cancer; opportunities for preventive action; and improved methodologies for the design and conduct of epidemiologic studies.

We continue to place great emphasis on the area of biochemical epidemiology in an attempt to stimulate collaborative studies between epidemiologists and laboratory scientists. To achieve this aim, the Program issued a request for cooperative agreement applications for research designed to develop, validate and apply laboratory-based biochemical markers of human exposure and susceptibility for use in cancer epidemiologic studies. It is estimated that five or six new studies resulting from this initiative will be funded this year, in addition to the seven studies under continuing support which resulted from our prior initiative.

AIDS Epidemiology: The Branch continues to encourage new investigators to undertake studies of the incidence and etiology of malignancies associated with human immunodeficiency virus (HIV) infection. A request for applications (RFA) was issued to stimulate epidemiologic research in the following areas: (1) increasing knowledge about the incidence of malignancies occurring in HIV-infected individuals; (2) increasing understanding of the specific mechanisms of carcinogenesis in HIV-infected individuals; and (3) increasing understanding of the relationships between immune status, genetic factors, HIV strains, co-infection with other viruses, acquired immunodeficiency syndrome (AIDS) treatments, and malignancy development. Several of the studies submitted in response to the RFA may be funded this year, and we anticipate reissuing the RFA in the coming year.

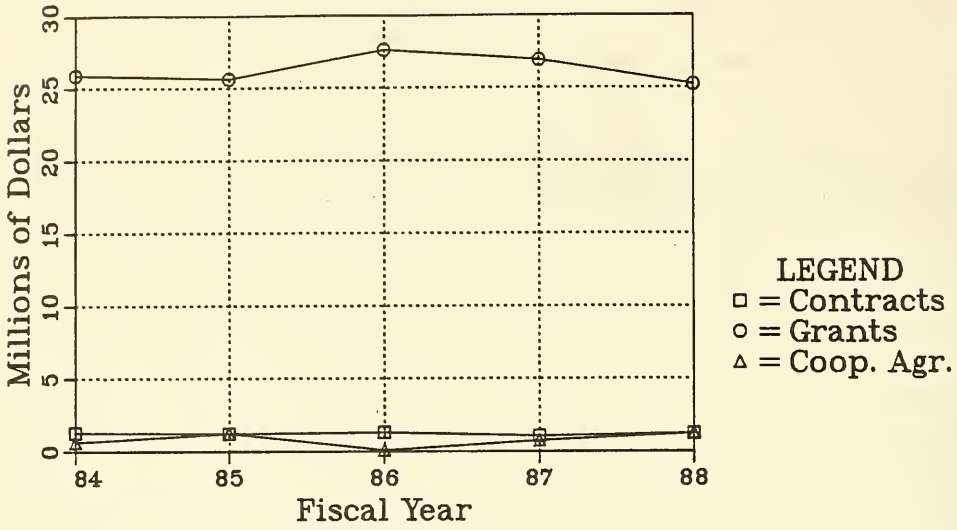
Small Business Innovation Research (SBIR) Program: The Branch continues to support the congressionally mandated Small Business Innovation Research Program designed to stimulate small business participation in Federal research and development projects. We have worked closely with intramural staff to develop a series of project statements

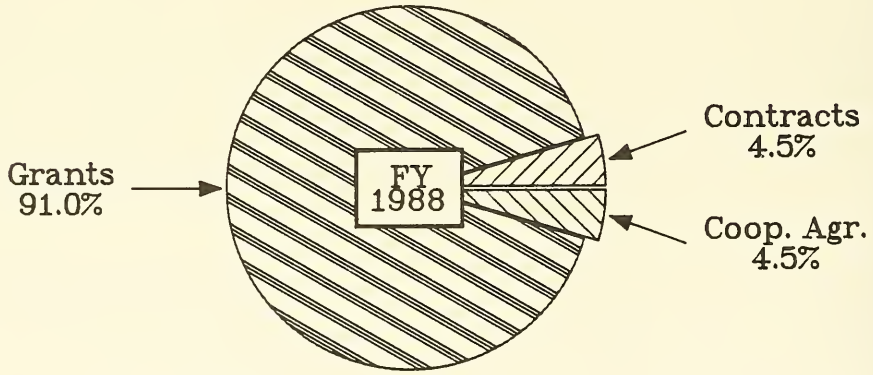
for activities suitable for small business efforts in epidemiology, biostatistics, and related areas. A number of these topics have resulted in grant or contract funded activities.

The following figures attempt to provide some perspective on the balance of activities within the Branch, as well as an overview of developments over recent fiscal years. As shown in Figure 1, the vast majority of our activities continue to be supported under the research grant mechanism.

Figure 2 illustrates the pattern of support for individual Branch program areas. The categories of AIDS-related epidemiology and biochemical epidemiology assumed separate identities in 1983; the first, because of the emergence of a serious epidemic, and the latter because of special research opportunities in this area.

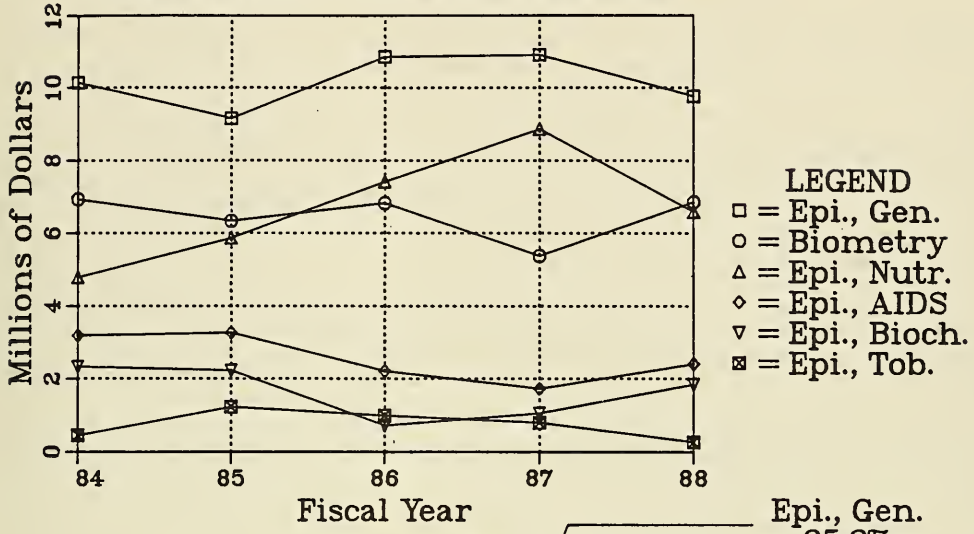
FIGURE I
EPIDEMIOLOGY & BIOSTATISTICS PROGRAM
EXTRAMURAL PROGRAMS BRANCH

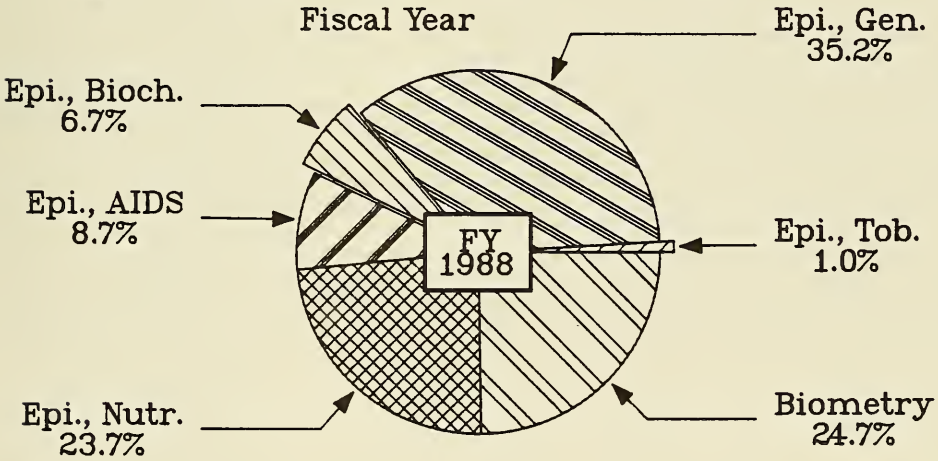




FISCAL YEAR 1988 ESTIMATE	$(Millions)	Percent
Contracts	1.25	4.5
Grants	25.24	91.0
Cooperative Agreements	1.26	4.5
TOTAL	27.75	100.0

FIGURE II
EPIDEMIOLOGY & BIOSTATISTICS PROGRAM
EXTRAMURAL PROGRAMS BRANCH





FISCAL YEAR 1988 ESTIMATE	$(Millions)	Percent
Biometry	6.86	24.7
Epidemiology, general	9.77	35.2
Epidemiology, biochemical	1.85	6.7
Epidemiology, AIDS-related	2.41	8.7
Epidemiology, nutrition-related	6.59	23.7
Epidemiology, tobacco-related	0.27	1.0
TOTAL	27.75	100.0

Description: The Biometry Program continues to foster and support research projects in the development of analytical tools for use by cancer epidemiologists. A decade ago, projects in the program could be classified into three mutually exclusive areas: theoretical statistics, computer science and pedigree analysis. Today the majority of the projects are interdependent collaborative efforts among groups working on allied projects. A substantial portion of the imputus for this change has been the rapid advancement of computer science and molecular biology. Developments in biomedical computing are now primarily in the private sector as it attempts to attract new markets. Hence, the Biometry Program stimulates dialogue among a diverse group of specialists that includes biostatisticians, basic scientists, clinicians and industrial scientists.

The Program continues to revolve around investigators possessing a combination of mathematical, statistical, and subject matter knowledge enabling them to project future statistical needs from the events of the present. In many cases, they identify discrepancies in existing statistical methods, devise methods to circumvent them, and refine or extend such methods for use with the more complex experimental designs now being proposed for the future. For instance, a drawback was noted in the proportional hazards model, long the standard method of analysis of continuous failure time data (effects of multiple risk factors on occurrence of disease). The model does not take into account the time dependence of binary outcomes (disease or no disease). For cohort studies it was deemed better to classify disease cases and person-years of observation jointly according to discrete categories of time, age, and risk factors. The resulting multidimensional matrix is amenable to analysis by log-linear Poisson regression when cases are formally specified to have independent Poisson distributions (15). Other examples would include the mathematical modeling currently getting underway to predict the incidence and infection rates of AIDS utilizing available data but preparing for future needs, recognizing that not all factors that need to be accounted for have as yet been determined (16,75).

In essence, all theoretical statisticians, whether involved in improving clinical trials, determining sample sizes necessary for given experiments, constructing methods for evaluating treatments, increasing patient accrual, handling missing data and loss to follow-up or reducing problems related to misclassification, covariate confounding or competing risks, must prove their techniques to be biologically as well as mathematically sound. For this reason, it is of paramount importance that they collaborate with basic scientists and/or clinicians in their respective areas of interest.

Similarly, as twin methods for genetic analysis gave way a decade ago to analysis of nuclear families, the latter, in turn, gave way to pedigree analysis. Improvements in statistical methodologies enabled human geneticists to move from testing for heritability of qualitative (dichotomous) to quantitative (continuous) characteristics. With recent advances in high-speed computer technology and molecular biology, there has been a merging of pedigree and gene linkage analyses. Genetic markers are used to test particular families (pedigrees) to see which allele of the marker signals the presence of the gene. Multiple markers are necessary to ensure the detection of the origin of the marker allele in a subject and to determine whether the subject carries the disease in question (140,150,180).

Analysis of genetic predisposition to cancer is a very complex problem. It will take a long time for statistical and medical geneticists to develop the necessary probes and mapping skills to detect the specific genetic abnormalities and/or mutagenic defects relevant to the problem (11,140). In addition to mapping, which can be very expensive, alternative technologies for measurement of mutations have been developed utilizing two-dimensional electophoresis and automated gel reading (53).

Research Accomplishments: Of greatest interest this year has been the finding that a gene responsible for von Recklinghausen's neurofibromatosis (NF) is located near the centromeric region of chromosome 17. Fifteen Utah kindreds were involved in this discovery. The analysis showed no evidence of heterogeneity, indicating that a significant proportion of NF cases are due to mutations at a single locus. Further genetic analysis is now underway to refine this localization as well as to identify and clone the defective gene. Since NF is one of the most common autosomal dominant conditions in humans (1 in 2500 to 3300) and affected individuals are at increased risk for a wide array of complications, including neoplasia, this finding offers promise for an increased understanding of the etiology and, more importantly, the possiblility of more effective treatment (11,140).

Utilizing the same genealogical data base, another investigator has successfully shown the autosomal dominant inheritance of susceptibility to adenomatous polyps (with allele frequency as high as 19 percent) in families ascertained through either a single proband or a cluster of colon cancer cases. The observation that all cases of either of these two phenotypes are genetic in origin is striking (chromosomal localization of the adenomatous polyp susceptibility gene by the detection of interstitial deletion on chromosome 5q). This study is now being enlarged for confirmation of these findings and for more intensive studies such as DNA marker linkage, detection of cancer mechanisms and gene-environment interactions (20).

Other genetic studies supported by the program are those concerned with kindreds of hereditary nonpolyposis colon cancer, familial atypical malignant mole melanoma, ataxia-telangiectasia and a number of childhood tumors (80,140,151,152,153). Bloom's syndrome continues to be studied on a case-by-case basis, with the total number of cases worldwide now numbering 130, with 96 surviving. In these 130 cases, 57 malignant neoplasms have been detected with the mean age at diagnosis just under 25. Bloom's syndrome is characterized by the high frequency and early age of cancers arising at a wide variety of sites (45).

Biostatisticians working with clinical trials appear to have reached a point where they feel the need to reevaluate their prior recommendations based on insights recently gleaned in trials (23,33,44,54,63,147,179). Specific problems have surfaced relating to the adequacy of Phase I/II designs, stopping rules, methods for combining data from multicenter studies, and generalization of results. The whole area seems ripe for much in-depth research by investigators familiar with the past and present performance of this basic research tool utilized for evaluating new therapy or untested existing methods.

Since results of Phase I studies are used in Phase II trials and Phase II results are used in Phase III trials, statisticians are taking a hard look at whether or not current Phase I/II designs are adequate to allow proper design and execution of the Phase III trial. Although it is acknowledged that critical information is based on the results of Phase III trials, the amount of statistical input into

the development of Phase I/II does not seem commensurate. There is little in the literature addressing either Phase I or Phase II methodology (33,44).

The current approach to Phase I trials is to enter small patient groups (three) sequentially at a series of prespecified dose levels. If no toxicity is seen at that level, then the next group of patients is entered at the next higher dose. The investigation gradually escalates. If toxicity is seen in one or more patients, then an additional group is entered at that level. If toxicity is confined to one of the six, then escalation may resume; otherwise, the trial stops and the next lower level is taken as the maximum tolerated dose (MTD). The statistical problem is one of estimating a percentile of tolerance distribution with respect to some definition of toxicity. The tolerance distribution is the distribution of individual doses that results in a defined level of toxicity in a population of patients. Some trials seek to determine this distribution directly, via dose escalation within individual subjects. Data obtained in this manner are subject to question as to whether or not observed toxicity is a result of the dose given, the cumulative effect of all the doses given or a gradual decline in the patient's condition. For this reason, the usual approach is to reconstruct the tolerance distribution by treating at a number of dose levels and observing the fraction showing toxicity at each dose level. The MTD is some percentile of the distribution at which, on the average, one out of three patients will experience toxicity of a specified degree. The drawback is that this design has no intrinsic property that makes it stop at any given percentile. It can only stop at one of the prespecified dose levels. The basic problem is not that the MTD will be wrong, but that the probability that it is wrong depends arbitrarily on the number and actual percentiles of the dose levels examined. Another important element missing from the traditional approach is a basis for accounting for sampling error in the estimate of MTD. This is because the distribution of stopping doses depends on an essentially unknown dose-response curve.

To improve the Phase I trial, it appears that statisticians should consider design and analysis as two distinct entities. The design (sampling scheme) is the mechanism for objectively determining the sequence of dose levels to be tested and analysis, the statistical technique for obtaining an estimate of the MTD and its sampling error. Various sampling schemes are now under consideration and their strengths and weaknesses should soon be summarized and published. Analysis methods will need to be revised and refined according to the sampling scheme deemed most appropriate (33,147).

The Phase II trial evaluates whether or not a new therapy is of sufficient activity to warrant further testing. The two main problems underlying it appear to be a need for 1) a clear definition of the objectives of the Phase II process (e.g., is it to estimate response rate to a specified precision, or to screen large numbers of therapeutic strategies and classify them as to their probable effectiveness?); and 2) a recognition that the typical Phase II study is small, hence, may not adequately represent the class of patients to be entered into a Phase III trial (33,147). This leads into multicenter clinical trials and what interpretation can be expected from studies where data are combined across strata into a single set. Biostatisticians are questioning the pooling process, considering issues such as differences in treatments and length of follow-up, and more importantly, differences in patients. The latter questions the assumption that patients from each center are at identical risk (stage of disease).

In terms of generalization of results, for a clinical trial that has no eligibility restrictions on patient entry, results can be generalized to the general population

of cancer patients. However, if only a small proportion of available cases are permitted to participate, any extrapolation of the results to the remaining cases must be viewed with skepticism. It is clear that problems of this sort only appear as results from clinical trials become available and an area such as extrapolation to the general cancer patient becomes a basis for optimal therapy (7).

Interagency agreements with the Social Security Administration and Internal Revenue Service are nearing termination. These agreements were to support efforts to develop a national resource for the investigation of cancer in the workplace. At the time the agreements were entered into, it was thought that they would result in the creation of public use tapes. After it became apparent that neither agency would be able to provide a public use tape, because of legal disclosure problems, the agreements were modified to require each agency to develop a methodology paper describing the difficulties in obtaining cooperation from state and other governmental agencies. These methodology papers should make a substantial contribution to the literature for others interested in pursuing occupational epidemiology along similar lines.

Projections: The advent of powerful computer work stations with interactive graphic capabilities is changing the nature of statistical practice and thus the Biometry Program. There should be a gradual shift from exploratory data analysis to more novel uses of numeric and graphic techniques in confirmatory analysis of issues such as robustness and prediction.

A broad range of statistical issues of importance to epidemiologic research have been proposed, approved, and funded during the year. In most cases, the investigators involved were already established in the Program; hence, many of the issues proposed are logical extensions of previous work (15,54,75,169). Other issues are in response to current public health problems. These studies should lead to publications, making results available to the scientific community.

The Biometry Program will continue to grow as investigators initiate new investigations relative to cancer etiology and epidemiology. Program staff will continue to work with prospective applicants to stimulate interest in utilizing their statistical skills in fields of biomedical research.

EPIDEMIOLOGY

Description: The cancer epidemiology extramural research program supports descriptive, analytic and methodologic studies. Inquiries into the natural history of neoplasia in humans, elucidation of the role of precursor and associated conditions, studies of the incidence, prevalence and mortality from human cancers, and examination of the geographic distribution or time trends are appropriately assigned to the program.

The program is particularly interested in analytic epidemiologic studies of host factors and environmental, occupational or life-style exposures, including a number of specific agents known or suspected to influence cancer risk. There is strong interest in supporting research which elucidates causal associations and mechanisms of carcinogenesis in human populations, as well as basic epidemiologic research which may provide information essential to preventive intervention.

In order to improve the specificity and accuracy of research findings, the program supports methodologic studies that relate to the design, conduct and analysis of

epidemiologic investigations, and that improve the capacity to distinguish contributions of multiple risk factors. This support includes the development and characterization of laboratory procedures. In 1982, a program in biochemical epidemiology was initiated to refine new measurement techniques and to encourage their subsequent use to study individual response to hazardous exposures, as well as to delineate high-risk groups. Twenty-two grants have been funded in response to three special initiatives issued by this program. However, in the intervening time, analytic epidemiologic investigations have progressed so that improved techniques of estimating risk parameters are usually employed. Therefore, the boundaries between biochemical epidemiology and general epidemiologic investigations have blurred. In response to this advance, the report of research progress is integrated this year. Similarly, the need to control for multiple exposures, which frequently include diet and use of tobacco products, has led to integration of the reports for tobacco-related epidemiology and diet and nutrition.

By and large, traditional research grants and program projects fund this epidemiologic research; however, since 1986, small grants have also been available for pilot projects, feasibility studies, test development and dissertation research support.

Research Accomplishments: A series of epidemiologic studies have suggested that Hodgkin's disease in young adults may have an infectious etiology. Case-control studies have revealed higher titers for Epstein-Barr virus (EBV) among cases, but could not determine if this infection occurred because of the lymphoma. To determine if EBV infection preceded the diagnosis of Hodgkin's disease (HD), the presence and levels of antibodies to a variety of EBV antigens in prediagnostic sera of HD cases were compared to similar values for appropriately matched controls. Sera from 240,000 presumably healthy persons free of HD were identified in 4 serum collections and followed through hospital records or cancer registries for the development of HD. For 43 cases, sera had been drawn and stored an average of 50.5 months prior to diagnosis; 96 controls who had been bled at the same time were identified. Significant elevations in cytomegalovirus antibody were not found. Overall, 57% of the cases had elevated titers to at least one EBV antigen, compared to 33% of the controls, RR = 2.9 (1.5-5.7). In general, the associations were stronger in the analysis of sera collected 3 or more years prior to diagnosis than in those collected in the 2 years immediately preceding detection of the disease. This pattern suggests chronic EBV replication occurring years preceding diagnosis. Whether EBV plays a direct role in pathogenesis or simply reflects a more fundamental factor affecting immune function is unknown.

The risk factors for cancer of the uterine cervix suggest a transmissible agent as its cause. For several years, herpes simplex virus type 2 (genital herpes) was considered the most likely candidate because women with cervical cancer were more likely to have elevated titers than women without cervical cancer. With improved virologic technology and understanding of viral carcinogenesis, human papillomavirus (HPV) has emerged as the most likely candidate, as reflected in this quotation from a paper published during the year: "HPV-6 and HPV-16 infect the squamous epithelium of the genital tract and are thought to be involved in the pathogenesis of benign and malignant lesions. HPV-6 is primarily found in benign condyloma whereas HPV-16 is present in dysplasias and in invasive squamous cell carcinomas." However, the expense and difficulty of diagnosing papillomavirus infection has limited information available about the distribution of viral infection in the population, the relationship of HPV infection to infection with other agents, and the natural history of the malignancy.

The strong collaboration among clinicians, pathologists, cytogeneticists, virologists and epidemiologists in the Seattle area is beginning to yield information of excellent quality on several topics and have promise of tremendous value in the future. A sample of 999 women, including 454 patients randomly selected from a sexually transmitted disease (STD) clinic and 545 consecutive college women undergoing annual examination, were examined for genital warts and tested for cervical HPV infection. Genital warts were found in 11% of STD patients and 2% of students ($p<0.001$), as would be expected in comparing women seeking medical care with those undergoing annual examinations. Similarly, the prevalence of other sexually transmitted diseases, including genital herpes, gonorrhea and trichamonas was at least two times greater among STD clinic women than student health clinic women. Genital warts were significantly associated with cervical HPV-6 or -11 DNA, but not with HPV-16, -18, or -31 DNA.

After excluding those women who may have sought medical care because of evident warts, HPV DNA or antigen was detected in cervical specimens in 10.6% of STD patients and 11.4% of students ($p = 0.73$), a similar percentage. In the STD clinic patients, the prevalence of cervical HPV DNA or antigen was highest at ages 16-19 and declined with increasing age. For students, the peak prevalence occurred at ages 20-24. Dysplasia of any severity was found in 53% of the women with HPV-6 or -11 infections, and in 41% of the women with HPV-16, -18 or -31. When the women with dysplasia and HPV-6 or -11 infections are taken as a group, none had severe dysplasia, while 21% had mild dysplasia and 32% had moderate dysplasia. Consistent with the idea that HPV types 16, 18 and 31 are associated with more severe forms of dysplasia, only 10% of the dysplasias in women infected with those types were mild, whereas 26% were moderate and 4%, severe. The investigators concluded that cervical HPV infection is prevalent among young sexually-active women and that infection by HPV-16, -18 or -31 occurs frequently in women who do not have cytologic evidence of HPV or dysplasia or evidence of papillomavirus antigen. Why the prevalence of cervical HPV infection is similar among college students and STD clinic patients, despite the fact that they are quite dissimilar in terms of risk for and prevalence of other STDs, is not known (62). Virologic research, carried out in close coordination with the clinical investigations outlined above, is developing better and less invasive diagnostic procedures.

The immunological response to HPV infections of genital epithelia is poorly understood because of the lack of purified viral antigens. In an effort to develop a source of HPV-encoded proteins, a series of plasmid constructs which express restriction enzyme fragments from the open reading frames (ORFs) of HPV types 6b and 16 DNAs have been made. These HPV DNA fragments are expressed in Escherichia coli (E. coli) as fusion proteins linked to a portion of the E. coli tryptophan E synthetase (trpE) gene product. The fusion proteins were purified and injected into rabbits to produce polyclonal antibodies, and the sera were tested in Western blot assays for their reactivity to the trpE protein and to fusion proteins containing the respective ORF. Several types of antibodies were obtained: many sera reacted with both the trpE and the ORF portions of the fusion protein, several sera reacted only with the HPV ORF, and some sera reacted largely with the trpE part of the fusion protein. An anti-E7 ORF (HPV-16) serum detected a protein of 15 kD in a cervical carcinoma cell line (CaSki), demonstrating the versatility of the antibodies (86).

The next step was to determine whether serum antibodies recognize bacterially expressed HPV fusion proteins, to identify which HPV antigens are targets of the humoral immune response and to verify and characterize observed reactivities of the HPV fusion proteins. In Western blot assays, the most striking reactivities present

in sera from patients with genital warts were to the HPV-6b major capsid antigen (proteins containing the L1 ORF). To a lesser extent, reactions were observed to L2, and in two cases to E2; no reactivities were seen with other HPV-6b constructs. Two sera reacted with the HPV-16 L2 fusion protein and 2 with the HPV-16 E4 protein. The antibodies directed against the HPV-6b fusion proteins showed no cross-reactivity with comparable regions of the HPV-16 ORFs. The investigators think this may indicate that infections with some types of HPV will be cross-protective, while other types will not be recognized, leading to multiple infections. This assay provides a useful approach for further studies of HPV serology (86).

When the polyclonal antisera directed against bacterially derived fusion proteins harboring different restriction fragments of the L1 and L2 ORFs of HPV-6b and HPV-16 were tested on tissues containing cervical intraepithelial neoplasia (CIN) and carcinomas, L1 ORF-specific antisera were not type-specific and detected the major capsid antigen in lesions infected with related HPV types. Anti-L2 ORF antisera could distinguish between HPV-1, HPV-6 and HPV-16 when the fusion protein used as the immunogen did not harbor the aminoterminus of the L2 ORF. The anti-L1 ORF antisera were employed to detect the major capsid protein in various lesions by immunohistochemical staining. Lesions harboring HPV-16 were positive in a high percentage (87%) of CIN types I-II, and less frequently in carcinomas in situ (CIS) (29%) or invasive carcinomas (17%). In all cases, capsid antigen expression was restricted to differentiated cells at the periphery of the lesion (87).

Several problems were overcome within the year. Antibodies directed against E. coli proteins were overcome by extensive preabsorption of the sera with large amounts of bacterial lysates. In sequencing the E5 ORF of HPV-16, these investigators discovered an additional nucleotide, a thymidine residue, at position 3903 compared with the sequence which was published in 1985. The additional T had two effects; first, in reading frame 2 in which the original E5 ORF was predicted, the additional T changed the reading frame downstream of position 3903 to create an ORF (designated E5*) that terminated at position 4018 and potentially encoded a 52-amino acid polypeptide. Secondly, in reading frame 3, a new ORF was created (positions 3807 to 4097), which is proposed as the authentic papillomavirus type 16 E5 ORF. It contained a methionine residue and encoded an additional 82 amino acids. Both ORFs have been cloned into bacterial expression vectors (pATH), and the fusion proteins have been used to generate polyclonal antibodies in rabbits (86).

Experimental research with human papillomaviruses has been inhibited by inability to culture the virus. There appears to be virus-specific interaction with keratinocytes, which is influenced by the stage of maturation of the host cells but is poorly understood. The development of transformed keratinocytes with integrated HPV DNA would permit experiments which could explain the observed distribution of viral DNA/viral replication in squamous epithelium. Progress has been made: Transformation studies have been performed on NIH-3T3 cells using concatemerized human papillomavirus type 6 and type 18 genomic DNAs. Cells were co-transfected with the pSV2neo plasmid to select cells taking up DNA and expressing transfected genes. Southern blots showed that foci selected for phenotypes associated with morphological transformation were all positive for HPV DNA retention and that the viral DNA was most probably integrated into cellular DNA. Some of the cell lines induced tumors in nude mice and these cell lines expressed viral RNA (86).

Primary human epithelial cells were co-transfected with pHPV 18 and pSV2neo, and cell strains generated. One cell strain (FE-A) which exhibits an extended life span

is currently in its twentieth passage. In comparison, control cultures can only be maintained up to the seventh passage. Southern blot analysis revealed the presence of at least one intact, integrated viral genome in these cells. FE-A cells show altered growth properties characterized by a change in morphology, clonal density and epidermal growth factor (EGF) independence. FE-A cells were also found to be defective in their response to terminal differentiation stimuli. Calcium and the tumor promoter, 12-O-tetradecanoylphorbol 13-acetate (TPA) treatment induce normal epithelial cells to differentiate, whereas the HPV-18 containing keratinocytes were resistant to these signals, indicating their partially transformed nature. These cells were not able to induce tumors in nude mice over a period of up to four months. A second cell strain FE-H18L, also generated by transfecting HPV-18, also exhibits an extended life span and similar alterations in morphology. Viral RNA transcribed from the early region of HPV-18 was detected in both cell strains by Northern blot analysis. These cell strains should provide a useful model for determining the role of HPV in carcinogenesis (86).

It has been suggested that cancers of the cervix, vulva and anus may share one or more risk factors. If this is true, women with cancer at one anogenital site would be at increased risk of developing another anogenital tumor. In an ongoing case-control study of residents of western Washington state, it was found that women with in situ or invasive vulvar cancer reported a history of prior or concurrent anogenital tumors far more frequently than did women in the control group. This association did not appear to be confounded by demographic variables or frequency of cervical screening. The data seem to reflect a common etiology, which is likely to be a sexually transmitted disease. It is conceivable that these tumors may be caused by different sexually transmitted diseases, several of which often occur in the same individual. Human papillomavirus has been found in tumor tissue from the cervix, vulva, vagina and anus. Several investigators have reported finding the same type of HPV virus in multiple anogenital cancers in the same individual. Genital herpes and smoking are two additional putative risk factors found more often among cases of cervical, vulvar and anal cancers than among controls. Whether herpes simplex virus type 2, HPV and smoking are independent risk factors or whether they interact with each other in the development of anogenital cancers remains to be clarified (28).

To elucidate the risk factors for anal cancer, epidemiologists in Seattle interviewed and obtained blood specimens from 148 persons with anal cancer and from 166 controls with colon cancer in whom these diseases were diagnosed during 1978-1985. In men, a history of receptive anal intercourse (related to homosexual behavior) was strongly associated with the occurrence of anal cancer (relative risk, 33.1). Anal intercourse was only weakly associated with the risk of anal cancer in women (relative risk 1.8). Among the subjects with squamous cell anal cancer, 47% percent of homosexual men, 28% of heterosexual men and 28% of women gave a history of genital warts, as compared with only 1-2% of controls and no patients with transitional-cell anal cancer. In patients without a history of warts, anal cancer was associated with a history of gonorrhea in heterosexual men (RR, 17.2) and with seropositivity for herpes simplex type 2 (RR,4.1) in women. Current cigarette smoking was a substantial risk factor in both women (RR, 7.7) and men (RR, 9.4). Conclusions drawn from those findings are that homosexual behavior in men is a risk factor for anal cancer and that squamous cell anal cancer is also associated with a history of genital warts, an association suggesting that papillomavirus infection is a cause of anal cancer. Certain other genital infections and cigarette smoking are also associated with anal cancer.

To identify risk factors for prostate cancer and to try to explain the high risk in blacks relative to whites, case-control interview studies of prostate cancer were conducted in both populations in southern California. Both studies included 142 pairs of cases and population controls matched on age. A past history of venereal disease was associated with increased risk of prostate cancer in both populations (relative risk (RR) = 2.3 in whites; RR = 1.7 in blacks). The result in blacks was statistically significant. Black cases tended to have more frequent sexual intercourse than black controls at all ages: the difference became statistically significant for intercourse late in life. Data from controls suggested that, overall, blacks have earlier and more frequent sexual activity than whites, but the two populations were dissimilar in social class characteristics. Fat intake was a risk factor for prostate cancer in both populations, but vitamin A consumption and protein intake were inconsistently related or unrelated to prostate cancer risk. While beta-carotene was not consistently related to risk, there was some indication that in persons with low fat intake, low beta-carotene intake may be associated with high risk. Circumcision was negatively associated with risk in both populations.

A population-based case-control study was conducted in men aged 60 or less to assess the risk of prostate cancer associated with vasectomy and other factors. Data were obtained from 216 case-control pairs by telephone interviews. The matched pairs' relative risk (RR) for vasectomy in ever married men was 1.4 with 95% CL 0.9-2.3. There was a positive association between the number of years since vasectomy and prostate cancer risk. Early age at first sexual intercourse was associated with increased prostate cancer risk but there were no consistent associations with number of sexual partners or frequency of sexual intercourse.

Cigarette smoking was also associated with increased risk of prostate cancer and there was a positive dose-response relationship with years of smoking. To determine whether the association with vasectomy might have a hormonal basis, the investigators compared levels of testosterone and testosterone-binding globulin capacity (TeBG-bc) in 33 of the vasectomized control men with levels in 33 non-vasectomized controls of the same age, weight and height. Testosterone levels were higher in vasectomized than in non-vasectomized controls. The ratio of testosterone to TeBG-bc (an index of bioavailable testosterone) was 13.5% higher in vasectomized men.

An epidemiologic study of thyroid cancer in women aged 40 and under was conducted to test the hypothesis that endogenous hormones may relate to the development of this disease, since the only known cause of thyroid cancer, ionizing radiation, does not account for the striking female over male excess. When compared to neighbor controls, women with thyroid cancer were more likely to have given a history of benign hyperplastic thyroid disease and were more likely to have been pregnant. Both of these findings were consistent with findings of previous studies. After eliminating women with a history of hyperplastic thyroid disease from the analysis, a strong association with miscarriage as the outcome of the first pregnancy was found (RR = 11.5), and this factor may be another indicator of thyroid abnormalities. An independent and increasing risk was observed with increasing gravidity after excluding women with prior thyroid disease and those whose first pregnancy ended in miscarriage. The RR for 4 or more pregnancies was 6.3. Prior exposure to radiation therapy was not an important factor in this study of young women (130).

Girls who engage in strenuous physical activity are often amenorrheic and have recently been reported to be at reduced subsequent risk of breast cancer. To

determine whether moderate amounts of exercise affect menstrual cycle patterns and ovulatory frequency, the menstrual cycles and physical activity patterns of 168 high school girls were monitored for a 6-month period. Anovulatory cycles were associated with later age at menarche, fewer elapsed years since menarche and greater levels of energy expended per week in physical activity. After adjusting for age at menarche and years since menarche, a significant co-related trend in the risk of anovular menstrual cycles was associated with increasing levels of physical activity. Major determinants of average cycle length were weekly average energy expenditure(<=750 kcal/wk associated with cycles that were on average 2.4 days longer), age at menarche (an increase of 0.7 days per year of age) and race (Asians having cycles about 1.9 days longer than Caucasians). Because the cumulative number of ovulatory cycles is associated with risk of breast and ovarian cancers, these data suggest that regular participation in moderate physical activity may provide an opportunity for the primary prevention of these cancers (130).

In postmenopausal women, obesity is positively related to the risk of both breast and endometrial cancer. Additionally, obesity is associated with increased estrogen production secondary to increased peripheral aromatization of endogenous androgens. In postmenopausal women, this effect is proportionately more significant because the ovaries no longer contribute to production of estrogen. Obesity also alters the further metabolism of estrogens, resulting in products that retain estrogenic potency. Consequently, the estrogen-sensitive tissues of obese women are exposed to more stimulation than those tissues in leaner women. It is possible that this increased estrogen exposure is responsible for the augmented risk of breast and endometrial cancer observed in obesity. Evidence is accumulating that dietary macronutrients can alter the metabolism and excretion of endogenous estrogen and androgen, providing a potential mechanism by which diet can modulate the risk of hormone-sensitive cancers (13).

In another study, urinary and fecal excretion and plasma estrogen levels were measured in pre- and postmenopausal women eating different diets. Comparison of women eating a "Western diet" containing high fat (40% of calories) and low fiber with age-matched vegetarians eating a moderate fat (30%) and high fiber diet revealed that the vegetarians excreted threefold more estrogens in their feces, excreted less estrogens in the urine and had 15-20% lower plasma estrogen levels. Correlation analysis of dietary components and plasma estrogen showed that plasma estrogen was positively associated with fat and was negatively associated with fiber. The results indicate that diet can alter the route of estrogen excretion by influencing the enterohepatic circulation which in turn influences plasma estrogen levels (48).

The effect of a high fat, low carbohydrate, low protein diet on the in vivo oxidation of 17 beta-estradiol was studied using radiometric methods. Because the range of fat content in the experimental diets exceeds the range of usual human dietary practices, this study was carried out in chimpanzees. Five male chimpanzees were fed a normal (13%) fat diet or a high (65%) fat diet for 8 weeks. After a 4-week rest period, the animals were fed the alternative diet. The mean percent oxidation of 16 alpha-[^{3}H]estradiol-17 beta 24 hours after injection was 3.8 $\pm$ 1.3% (SD) on the normal diet vs. 18.4 $\pm$ 4.7% on the high fat diet. In contrast, the mean percent oxidation of 2-[^{3}H]estradiol 24 hours after injection was 31.6 $\pm$ 3.8% on the normal diet vs. 20.0 $\pm$ 3.5% on the high fat diet. These results suggest that the oxidation of 17 beta-estradiol to estriols relative to that to catechol estrogens is increased by a high fat diet (13).

The prevalence of several known or suspected risk factors for breast cancer is changing among young women. The time trend in incidence of breast cancer among young women in western Washington was analyzed as a possible predictor of trends in future incidence rates. Data were from the Seattle-Puget Sound Surveillance, Epidemiology and End Results cancer registry. For women aged 25-44 years (n=1,869 cases), the incidence of breast cancer increased by 22% between the time periods 1974-77 and 1982-84. The estimated annual increase was 2.5%. The increase in incidence over time appeared to be greater among those residing in low-income census tracts of urban counties and among black women. Trends of risk factors for breast cancer (delay in childbearing, decline in age at menarche, fewer children per woman, lower fat diet, oral contraceptive use and abortion before first-term birth) must be considered as possible contributors to the increasing risk of breast cancer in young women. Because there has been a recent trend toward delay of childbearing in the U.S., women in the birth cohort of 1945-49 will have an estimated 5% greater incidence of breast cancer, and those in the cohort 1950-54 an estimated 9% greater incidence compared with the cohort of 1935-39, which had the distribution of age at first birth most favorable for breast cancer risk (30).

Hormonal factors appear to be involved in ovarian cancer as well. Analyses of the combined data from two case-control studies of epithelial ovarian cancer (combined total: 299 cases and 1,032 age and race matched controls) conducted in the San Francisco Bay area between 1974 and 1985 were consistent with other studies in finding increased risks of ovarian cancer associated with nulliparity and menarche at an early age. The protection afforded by oral contraceptive use increased with increasing duration of use, and with time since first use after adjustment for duration of use. No associations were found for time since last oral contraceptive use, age at menopause or age at first full-term pregnancy among the parous. Reproductive characteristics and oral contraceptive use were combined to estimate a woman's total number of ovulations, which was positively associated with ovarian cancer risk, supporting the conjecture that ovulation or concomitant endocrinologic phenomena increases a woman's risk for ovarian cancer.

Cancer of the ovarian epithelium has been noted to occur more commonly in women who have spent many of their reproductive years in marital-type relationships without birth control, and in women estimated to have ovulated for many years. Interrelationships between these characteristics and their combined effects on ovarian cancer were explored in a case-control study of 188 women with histologically confirmed epithelial ovarian cancer and 539 control women. Multivariate analyses revealed that time at risk of pregnancy was associated with a twofold increase in risk independent of parity, oral contraceptive use, and estimated years of ovulation. While cancer risk exhibited a twofold range from lowest to highest years at risk of pregnancy and a fourfold range from lowest to highest years of ovulation, risk among women in the highest categories of both these characteristics was estimated to be eight times that of women in the lowest joint category. Some abnormality of ovulation that reduces the likelihood of conception may increase risk of epithelial ovarian cancer.

To investigate whether blocking the entry of particulates such as talc protects against ovarian cancer, histories of talcum powder use, tubal sterilization, and hysterectomy with ovarian conservation in 188 women with histologically confirmed epithelial ovarian cancers were compared with similar histories in 539 control women. Ninety-seven (52%) of the cancer patients habitually used talcum powder on the perineum, compared to 247 (46%) of the controls. Adjusted for parity, this

difference yielded a relative risk of 1.40. There were no statistically significant trends of increasing risk with increasing frequency or duration of talc use, and patients did not differ from controls in use of talc on sanitary pads, contraceptive diaphragms or on any combination of pads, diaphragm and perineum. Fewer ovarian cancer patients (7%) than controls (13%) reported prior tubal sterilization, a difference that persisted when subjects were stratified by parity status. The relative risk associated with tubal sterilization, adjusted for parity, was 0.56. Similarly, fewer patients (20%) than controls (28%) reported prior hysterectomy. This difference yielded a relative risk of 0.66. The protective effect of hysterectomy was confined to those who underwent this surgery ten or more years prior to interview. These observations are consistent with a causal role for genital exposures to environmental agents. Nevertheless, sterilization and hysterectomy may protect by altering some concomitant of ovarian function, and the role of talc in ovarian cancer remains unclear.

Relationships between ovarian cancer and lifetime consumption of coffee, cigarettes and alcohol were also examined in the case-control study cited above. None of several measures of lifetime consumption of cigarettes and alcohol differed significantly between cases and controls. By contrast, 11 (6%) of the cases never regularly consumed coffee, compared to 31 (11%) of the hospital controls and 26 (10%) of the population controls. Adjusted for smoking, these differences yielded an odds-ratio of 2.2 for the comparison based on cases vs. all controls. Statistically significant trends of increasing risk with increasing duration of coffee consumption were evident when cases were compared both to hospital and to population controls. Overall, ovarian cancer risk among women who had drunk coffee for more than 40 years was 3.4 times that of women who had never regularly consumed the beverage. However, the data exhibited no clear trends in risk with increasing frequency of usual daily consumption, or with increasing total consumption, estimated by multiplying usual frequency in cups per day by duration of consumption in years. Odds-ratios relating duration of coffee consumption to ovarian cancer were not altered by adjustment for several characteristics associated with the disease. Nevertheless, further investigation is needed to exclude potential confounding by other unmeasured characteristics.

Results from a prospective study initiated in 1979 to investigate the adverse health risks associated with smoking low tar and/or low nicotine cigarettes were recently published. Approximately 100,000 residents of the San Francisco Bay area, who were members of the Kaiser Permanente Medical Care Program, completed a questionnaire describing smoking practices during multiphasic health checkups. In general, the participants were better educated and more health conscious and, thus, not a representative sample of the Bay Area population. Overall, the prevalence of current smoking was slightly higher in men than in women aged 30 years and above, but in those younger than 30, the reverse was true. In every age group, however, female smokers were apt to smoke fewer cigarettes per day, to inhale less and to smoke cigarettes with lower tar and nicotine yield. Racial differences in the prevalence of smokers were more striking than sex differences. Among the racial groups, blacks showed the highest percentage of smokers, whites were second highest and Asians the lowest with Asian women being substantially lower than other race-sex groups. On average, whites smoked more cigarettes per day and inhaled more smoke than blacks; whites were more likely to smoke low-yield cigarettes than blacks. Compared with a 1964 to 1968 study in the same setting, there were small downward trends in the prevalence of cigarette smoking in men and white women and in the prevalence of heavy smoking among male smokers during the 1979 to 1984

period. However, there was no apparent increase in the use of lower-yield cigarettes by smokers. National trends from the mid-1960s to the early 1980s in the prevalence and amount of smoking were generally similar to those found in this study population (43).

Published epidemiologic studies have reported an association between cigarette smoking and cancer of the uterine cervix. A pilot study was recently conducted to determine whether there was any correlation between mutagenicity of a woman's uterine cervical mucus and her current smoking status. Of 36 current smokers, 14 (39%) had positive mutagenicity tests as compared to 5 of 42 (14%) nonsmokers. These findings need to be replicated in a larger study (60).

In experimental animals and cultured human cells, the majority of mutagenic and carcinogenic compounds are metabolically activated to electrophilic species which interact with DNA, RNA or protein to form covalent adducts. Such binding appears to be a critical early event in chemical carcinogenesis. A general and sensitive approach for the measurement of DNA lesions in human white blood cells and tissues exposed to occupational or environmental mixtures of genotoxic compounds was recently published. The basic procedure entails enzymatic cleavage of the DNA preparation to 3'-mononucleotides, labeling with ^{32}P followed by resolution on thin-layer chromatography plates. The ^{32}P-labeled adduct fractions are detected as extra spots and are quantitated by scintillation counting. This technique is being applied to analyze samples obtained from human subjects exposed to polycyclic aromatic hydrocarbons, arylamines and derivatives, azo compounds, formaldehyde, styrene, cigarette smoke and volatile pollutants generated by wood burning stoves. This assay enables the detection and quantitation of most aromatic and bulky nonaromatic adducts at frequencies as low as 1 lesion per 10^{10} DNA nucleotides (124). An alternate approach currently being developed to quantitate DNA lesions is the electrophore post-labeling technique which does not use radioactive materials. Methodology involves quantitation by gas chromatography and detection by negative chemical ionization mass spectrometry. This technique is currently being used to analyze DNA adducts in biological samples obtained from cancer patients treated with alkylating agents, medical students and embalmers exposed to formaldehyde, and hospital workers exposed to ethylene oxide (47).

Studies of diet in relation to disease offer methodological challenges far more complex than most epidemiological investigations. Diet is not a single exposure, but rather a set of continuous variables. These variables interact with each other and are likely to have nonlinear relationships with disease. It has been questioned whether useful measurements of individual diets could be made within populations due to homogeneity of food intake and imprecision of assessment methods. Nevertheless, several studies in recent years have demonstrated reasonable levels of correlation between structured food frequency questionnaires and detailed assessment of diet. For a limited set of nutrients, biochemical measurements provide an alternate means of exposure assessment.

Interest in the role of diet in the etiology of human cancer has been stimulated by international studies in which large differences in cancer incidence rates were found between countries. A major problem in interpreting these correlational studies is that many factors other than dietary differences distinguish countries with a high cancer incidence from those with a low incidence. Genetic predisposition, itself, does not account for the international variations in cancer rates. This statement is based on studies of migrant populations and of secular trends within countries. Generally, populations migrating from an area with its own pattern of

cancer incidence rates acquire rates characteristic of their new location, although, for a few tumor sites, this change occurs only in later generations. The challenge for researchers studying the relation between diet and cancer is to identify the specific dietary determinants of cancer and to quantify their effects.

The population of Hawaii is multiethnic. The various racial groups have different dietary patterns and different rates of occurrence of the various neoplasms. Within ethnic groups, there is considerable variation in duration of residence in Hawaii, with some individuals being migrants and others being second or third generation native born. A valuable feature of this population is that out-migration rate is very low. An ongoing epidemiologic study of this population continues to explore the relationship of diet to the etiology of cancer, as well as the adequacy of dietary assessment methods. Preliminary data from the cohort study suggest an inverse relationship between consumption of fresh, raw fruits and vegetables and risk of colon cancer in males, but not in females. Data from the case-control study of lung cancer indicate odds ratios increasing with daily cholesterol consumption for men only, and in Japanese, Caucasians and Filipinos, but not in part-Hawaiians. This observation was noted in both light and heavy smokers and was stronger for squamous than adenocarcinomas. A number of case-control studies have been recently initiated. These studies will explore the relationship of dietary fat and vitamin A with endometrial cancer; relationship of dietary vitamins A, C and E and selenium with risk of cutaneous malignant melanoma; intake of dietary fat, fiber, calcium and energy balance with risk of colorectal cancer; and development of a telephone interview method for quantitative diet history assessment (72).

A prospective study of 18,000 men, aged 45-64, living in Shanghai, People's Republic of China, was recently initiated. The objectives of this study are to determine (1) the role of hepatitis B virus and aflatoxin exposure in the etiology of liver cancer; (2) the relationship between intake of salt, nitrate, N-nitroso compounds, and vitamin C deficiency and risk of stomach cancer; (3) the effect of cigarette smoking, alcohol consumption, intake of N-nitroso compounds and beta-carotene/vitamin A deficiency on the risk of esophageal cancer; (4) the interactive role of beta-carotene/vitamin A deficiency with cigarette smoking on the etiology of lung cancer. Detailed dietary histories and blood and urine samples will be collected on each subject (132). It is also planned to collect food samples at each season during a period of one year to determine aflatoxin contamination levels (123).

Data from the Western Electric Health Study were recently analyzed to determine the correlation of dietary and other risk factors with cancer incidence. The participants were men who were 40-55 years of age at the time of the baseline examination in 1957-58. The examination included family and medical history, physical examination, dietary history and measurement of blood pressure and serum cholesterol. It was found that a pattern of continuous large gains in weight from age 20 to 40 was associated with increased risk of death from cancer. After adjustment for age, serum cholesterol concentration, systolic blood pressure, cigarette smoking and alcohol intake, the relative risk of cancer death was 3.0. When body mass index was added to the model, the relative risk increased to 3.4. When the data were analyzed for risk of colon cancer, it was not clear whether the association with weight gain was due to fatness *per se*, to dietary factors associated with weight gain (for example, a diet with greater proportion of calories from fat), to decreased physical activity, or to some interaction of these factors.

The colon cancer rate in Utah is lower than the national average. In a recently completed case-control study, a comprehensive food frequency instrument was used to

obtain average daily intake of food five years prior to diagnosis. Cases reported higher daily food intake as measured by total energy content of the diet. Higher risk of colon cancer with increasing energy intake was found to be independent of stage of disease at diagnosis and obesity. Fat, protein and carbohydrate intake all had elevated relative risks but could not be assessed as risk factors independent of energy intake because of their strong correlations with total calories (99).

Projections: There is a need for studies of populations that have differing proportions of their energy coming from different components of the major nutrients to see if it is possible to delineate an independent effect for any of the macronutrients. There is also a need for stimulation of research designed to identify, characterize and validate markers of present or past dietary intake which could be useful in the conduct of nutritionally focused studies in cancer epidemiology. Further studies in population groups that are discordant with current dietary hypotheses may provide a better understanding of the etiology of human cancer. In recent years, smokers are shifting toward smoking filter-tipped cigarettes, especially those with low tar and nicotine yields. Careful monitoring of health status of smokers may provide a better understanding of trends in tobacco-related diseases.

To stimulate more collaborative studies between epidemiologists and laboratory scientists, a request for cooperative agreement applications for research designed to develop, validate and apply laboratory-based biochemical markers of human exposure and susceptibility was reissued in September 1987. Thirty-one applications, received in response to this announcement, will be reviewed by a special study section. It is hoped that several of these studies will be funded in this fiscal year.

AIDS-RELATED EPIDEMIOLOGY

Description: This program emphasizes the identification of risk factors and etiologic mechanisms for the AIDS and AIDS-associated malignancies, as well as clarification of the relationship between malignancies and HIV. While grants and cooperative agreements provide most of the support for these activities, the Branch continues to collaborate with the National Institute of Allergy and Infectious Diseases (NIAID) to support contracts for the study of the natural history of HIV infection in homosexual men (182,187,188).

Research Accomplishments: Risk Factors for HIV Infection and Disease Progression (182,187,188): The program continues to collaborate in the Multicenter AIDS Cohort Study (MACS). Five thousand asymptomatic homosexual men (from Baltimore, Chicago, Los Angeles, and Pittsburgh) were recruited in the spring of 1984 and are being followed semiannually for the development of AIDS, AIDS-related symptoms, and malignancies. Biological specimens, including serum, plasma, urine, semen and throat washings, are collected from participants at each examination. The stored specimens are available for use by interested investigators.

The decline in T4 lymphocytes in 1828 seropositive MACS participants was studied over 2 years. The following covariates had significant predictive power for estimating the decline in T4 cells: previous number of T4 cells; increases in T8 cells and IgA levels; and decreases in platelet count, hemoglobin, and HIV antibody levels.

Blood samples for flow cytometry studies were obtained from MACS participants. Although the T4 population decreased upon seroconversion, two subsets increased:

activated T4 cells and inducers of suppression (2H4-positive cells). The T8 population expanded upon seroconversion, and certain subsets increased disproportionately--activated T8 cells, and cells stained singly with 4B4 and 2H4. The number of receptors on the lymphocyte surface for DR and TQ-1/Leu-8 on both T4 and T8 cells also showed changes.

Twenty-two MACS participants were found retrospectively to have converted to HIV seropositive status during a six-month interval. Each seroconverter was matched to two seronegative and two seropositive controls. Matched case-control analyses showed that the following symptoms lasting for 3 or more days were associated with new HIV infection: fever, swollen lymph nodes, night sweats and headaches. It was notable that the majority of seroconversions were not associated with any symptoms lasting for 3 or more days.

Four of nearly 2000 prevalent seropositive subjects in the MACS cohort appear to have reverted from positive to negative by the HIV enzyme-linked immunosorbent assay (ELISA) test accompanied by corresponding changes in the Western blot tests. All initially had multiple bands by Western blot, which completely disappeared in three subjects and selectively disappeared in one. All sera were negative for p24 using an antigen detection test. Polymerase chain reaction is to be used to search for integrated retroviral sequences.

Incidence of Kaposi's sarcoma (KS) and non-KS AIDS was observed in the MACS cohort. Diagnoses were ascertained according to CDC surveillance definitions. The overall incidence was approximately constant. However, the proportion of cases that were KS systematically decreased over time. Initial analysis of possible explanatory variables suggested that KS cases had reported more frequent receptive anal intercourse at the study examination two years prior to diagnosis.

HIV-Associated Immune Alterations: The significance of antilymphocyte antibodies in patients with AIDS and their sexual partners was investigated. Eight of 10 patients with AIDS and 6 of their 10 partners had significant levels of antilymphocyte antibodies which were reactive with B- and T-cells. The 4 partners who had no detectable antibodies to HIV also had no antilymphocyte antibodies. Lymphocytotoxic antibodies may be responsible in part for lymphopenia.

HIV-Associated Malignancies: A case-control study comparing KS AIDS cases to AIDS cases with opportunistic infections (OI) was recently completed. Analysis showed that KS cases had higher T4:T8 ratios, were more likely to have antibodies to hepatitis B surface antigen, and were less likely to have been vaccinated for hepatitis B than the OI cases. KS cases were more likely to report the swallowing of semen, and were less likely to report venereal warts or cytomegalo virus (CMV) infections than OI cases.

Projections: The Branch continues to encourage new investigations of the incidence and etiology of malignancies associated with HIV infection. An RFA was issued entitled "Epidemiologic Studies of HIV-Associated Malignancies." The RFA was planned to stimulate epidemiologic research in the following areas: (1) knowledge about the incidence of malignancies occurring in HIV-infected individuals; (2) understanding the specific mechanisms of carcinogenesis in HIV-infected individuals; and (3) understanding the relationships between immune status, genetic factors, HIV strains, co-infection with other viruses, AIDS treatments, and malignancy development. Several new studies submitted in response to the RFA may be funded this year.

It is anticipated that these studies will provide critical information on the incidence, distribution and mechanisms of development of these retrovirus-associated cancers.

SMALL BUSINESS INNOVATION RESEARCH (SBIR) PROGRAM

Description: The Extramural Programs Branch continues to foster the goals of the Small Business Innovation Development Act of 1982 which seeks to stimulate the development and commercialization of novel approaches contributed by small, especially minority-owned and disadvantaged, businesses. This legislation was recently extended through FY93. The implementation of the SBIR program at NIH is unique since it is the only Federal agency in which both grant and contract mechanisms are used. The former has been available since the program's inception in FY83, the latter since FY85. Both mechanisms are subject to peer review procedures. Grant applications are accepted three times a year (April, August and December), while contract proposals may be submitted only once a year (December). Grants may deal with a wide variety of investigator-initiated topics including, but not limited to, those listed in the grant solicitation. Contract proposals, on the other hand, must be responsive to fairly specific programmatic topics listed in the contract solicitation. Interestingly enough, the focal point for the majority of submissions to our program area for both mechanisms has been microcomputer software (two phase I grants, one phase II grant, and two phase II contracts). Additionally, there are two phase II contracts that deal with the detection of carcinogen metabolites in mammalian systems.

Research Accomplishments: Of the three SBIR grants active during this fiscal year, one phase I and one phase II were funded in FY87. The remaining grant was the only fundable application of the 14 phase I grant applications submitted during FY88. As mentioned earlier, all three projects concern microcomputer software development. The ongoing phase II grant (89) deals with the extension of the exact analysis of categorical data from unstratified to stratified populations and from two-sample to k-sample problems. The resulting new techniques are expected to substantially improve the stratified linear rank, Kruksal-Wallis, Jonckheere-Terpstra, as well as other non-parametric tests. Software will be made available for a number of commonly used statistical software packages as well as a stand-alone version. The same investigator also has a phase I effort (90) dealing with the analysis of longitudinal studies (e.g., repeated tumor marker measurements, animal bioassays for tumor growth, and weight change during treatment). While past analyses handled such data parametrically based on unverifiable assumptions, recent non-parametric advances allow rigorous analysis of the data even with missing observations and time-dependent covariates. The investigator is unifying these new procedures into a user-friendly package which may prove especially useful for the analysis of time-dependent biological data from epidemiologic studies and quantifying exposure to tobacco smoke. The final phase I grant (70), recently funded, proposes the development of a cancer mapping system which could be used to compare high cancer incidence in various geographical areas with environmental or occupational data from the same areas. By comparing time-sequential incidence snapshots from the same geographical areas, changes in incidence trends within local and regional populations could be detected. The investigator plans to interface this new system with the Statistical Analysis System (SAS).

There are, at present, four active phase II SBIR contracts, one of which was just awarded. This new effort (183) is concerned with the development of a monoclonal

antibody detection system for Acrolein:DNA adducts in body fluids. One other phase II project (185) also is concerned with developing a detection system. The methodology involves identification of pesticides and their metabolites in mammalian systems by means of supercritical fluid chromatography. Substantial success with detecting aldicarb and carbaryl at subnanogram levels in rat hepatocyte preparations has been achieved. The remaining phase II contracts involve development of microcomputer software packages--one (181) is bibliographic, the other (186) is statistical. The first package allows the user to enter citation details into a common data base through a user-modifiable default format, then subsequently output selected references in the journal format of choice as supplied by the program. The second package is an advanced statistical program of considerable power and user-friendliness. This project is of particular interest inasmuch as it epitomizes the goals of the SBIR program. Although this package is still in development and the contract has 4 more months to run, a pre-release version of the software, known as EGRET, is for sale ($495). Ten orders have been shipped and more are in process. It has been exhaustively tested by experts around the world and used successfully in academic survival analysis classes. A major Federal agency is inquiring about a site license for its 2000 machines at various locations. Furthermore, it includes EPIXACT ($99), an optional exact procedures module developed by an SBIR-supported collaborator, that is universally requested with the package.

Projections: Based on the President's budget, NCI is likely to spend $20.0 million in SBIR program awards during FY89. While the quality of SBIR grant applications and contract proposals has increased steadily since the program's inception, initial technical review has also become more stringent so that the percentage of fundable projects has remained consistently low (no more than two grants per year). The contract side of the SBIR effort has fared somewhat better (five to ten awards per year), except during FY87 when no contract topics were advertised from this program area. Nevertheless, those projects that survive phase I review and manage to convert to phase II funding speak well for the goals of the SBIR program. It is projected that two phase I grants and seven phase I contracts will be awarded by the end of FY88. Topics addressed by the currently pending proposals include microcomputer generation of statistical tables, the use of bar codes for inventory and control of NCI repository specimens, and the production of purified human T lymphotropic virus-I (HTLV-I) envelope protein by recombinant technology. The Extramural Programs Branch remains eager to pursue funding of any meritorious projects that fall within its SBIR purview.

EXTRAMURAL PROGRAMS BRANCH

GRANTS ACTIVE DURING FY 88

Investigator/Institution/Grant Number	Title
1. ADAMI, Hans-Olov University of Uppsala 5 R01 CA 40264-02	The Risk for Gastric Cancer After Partial Gastrectomy
2. ANDERSON, Harold D. Stephens College 1 R15 CA 41999-01A2	Trace-Element Nutrition & Cancer Etiology
3. AUSTIN, Harland D. University of Alabama, Birmingham 5 R01 CA 39733-04	Case-Control Study of Endometrial Cancer & Obesity
4. AWERBACH, Tamara E. Harvard University 5 R01 CA 37820-05	Mathematics of Diffusion Assays--Mutagens & Antibiotics
5. BARTSCH, Helmut Internatl. Agency Res. Cancer 5 U01 CA 43176-02	DNA Damage as a Marker of Exposure to Betel Quid/Tobacco
6. BARTSCH, Helmut Internatl. Agency Res. Cancer 1 R13 CA 44878-01	Detection Methods for DNA-Damaging Agents in Man
7. BEGG, Colin B. Dana-Farber Cancer Institute 5 R01 CA 35291-06	Treatment Allocation in Sequential Clinical Trials
8. BEGG-MARINO, Lisa University of Pittsburgh 1 R01 CA 44751-01A2	Epidemiology of Obesity, Sex Hormones & Breast Cancer
9. BERKOWITZ, Gertrud S. Mt. Sinai Sch. Med. 5 R29 CA 47053-02	Prevalence & Epidemiology of Cryptorchidism
10. BERNSTEIN, Leslie Univ. of South Calif. Sch. Med. 5 R01 CA 44546-02	A Case-Control Study of Breast Cancer in Young Women
11. BISHOP, David T. University of Utah 5 R01 CA 36362-05	Linkage Analysis & Multiple Loci
12. BLUMBERG, Baruch Institute for Cancer Research 3 P01 CA 40737-03S1	Cancer Clinical Research at the Fox Chase Center - HBV & PHC

13.	BRADLOW, H. Leon Rockefeller University 5 RO1 CA 39734-04	Obesity, Diet, Estrogens & Cancer Risk
14.	BRANDSMA, Janet L. Long Island Jewish-Hillside Med. Ctr. 5 RO1 CA 39172-03	Cancers of the Head & Neck: Epidemiology & Biochemistry
15.	BRESLOW, Norman E. University of Washington 5 RO1 CA 40644-03	Statistical Methods in Cancer Epidemiology
16.	BROOKMEYER, Ronald S. Johns Hopkins University 1 RO1 CA 48723-01	Development & Application of Statistical & Quantitative Methods in AIDS Research
17.	BUCKLEY, Jonathan D. University of Southern California 5 RO1 CA 38908-03	Epidemiology/Biology of Childhood Non-Hodgkins Lymphoma
18.	BUFFLER, Patricia A. University of Texas Hlth. Sci. Ctr. 5 RO1 CA 32584-05	CNS Tumors & Occupational Exposures
19.	BUFFLER, Patricia A. University of Texas Hlth. Sci. Ctr. 2 RO1 CA 34448-04	Occupational & Environmental Exposures in the Etiology of Adult Leukemia
20.	BURT, Randall W. University of Utah 5 RO1 CA 40641-03	Inheritance of Discrete Colorectal Adematous Polyps
21.	BUZZARD, I. Marilyn University of Minnesota Mnpls.-St.Paul 2 RO1 CA 36522-04	Microcomputer-Based Dietary Data Collection Systems
22.	CAMPBELL, T. Colin Cornell University Ithaca 5 PO1 CA 33638-05	Diet & Cancer in China
23.	CHEN, Hubert J. University of Georgia 5 RO1 CA 40702-03	Selection & Estimation Procedure for Medical Treatment
24.	COMSTOCK, George W. Johns Hopkins University 5 RO1 CA 36390-05	Serologic Precursors of Cancer
25.	CORREA, Pelayo Louisiana State Univ. Med. Ctr. 5 PO1 CA 28842-08	Etiologic Studies of Gastric Carcinoma

26.	CORREA, Pelayo Louisiana State Univ. Med. Ctr. 5 R01 CA 40095-03	Lung Cancer in Non-Smoking Women
27.	CRAMER, David W. Brigham & Women's Hospital 5 R01 CA 42008-03	Correlates of Ovarian Cancer Risks
28.	DALING, Janet R. Fred Hutchinson Cancer Res. Ctr. 5 R01 CA 35881-05	Vulvar Cancer--Epidemiology, Biochemistry & Immunology
29.	DALING, Janet R. Fred Hutchinson Cancer Res. Ctr. 5 R01 CA 41410-03	Epidemiology of Penile & Urethral Cancer
30.	DALING, Janet R. Fred Hutchinson Cancer Res. Ctr. 5 R01 CA 41416-03	Breast Cancer in Relation to Prior Induced Abortion
31.	DAVIS, Scott Fred Hutchinson Cancer Res. Ctr. 5 R03 CA 44711-02	Methodologic Issues Related to Random Digit Dailing
32.	DAVIS, Scott Fred Hutchinson Cancer Res. Ctr. 5 R03 CA 45684-02	Nutritional Factors & Cancer of the Pancreas
33.	DE METS, David L. University of Wisconsin, Madison 5 R01 CA 18332-14	Statistical Problems in Cancer Research
34.	ELSTON, Robert C. Louisiana State Univ. Med. Ctr. 5 R01 CA 28198-09	Statistical Genetic Analysis for Cancer Families
35.	FIALKOW, Philip J. University of Washington 5 R01 CA 16448-13	Human Cancer -- Origin & Genetic Markers
36.	FILIPOVICH, A. H. University of Minnesota 1 R13 CA 39479-01A1	Conference on the Role of Immunodeficiency in Cancer
37.	FILIPOVICH, A. H. University of Minnesota 5 U01 CA 44120-02	Extramural Utilization of the Immunodeficiency Cancer Registry
38.	FINKELSTEIN, Dianne M. Massachusetts General Hospital 5 R01 CA 47048-02	Carcinogenicity Experiments for Environmental Health

39. FISCHL, Margaret A.
University of Miami
5 R37 CA 34988-06
Heterosexual & Household Transmission of HTLV-III

40. FOLSOM, Aaron R.
University of Minnesota
5 R01 CA 39742-04
Distribution of Body Fat & Cancer Risk in Women

41. FRASER, Gary
Loma Linda University
5 R01 CA 14703-14
Cancer Epidemiology in Adventists - a Low Risk Group

42. FRIEDMAN, Gary D.
Kaiser Foundation Res. Inst.
5 R37 CA 19939-12
Drug Surveillance: Cancer & Other Adverse Effects

43. FRIEDMAN, Gary D.
Kaiser Foundation Res. Inst.
5 R01 CA 36074-04
Are Low-Yield Cigarettes Less Hazardous?

44. GELLER, Nancy L.
Sloan-Kettering Institute
5 R01 CA 43074-02
Statistical Methods for Cancer Clinical Trials

45. GERMAN, James L.
New York Blood Center
5 R01 CA 38036-05
Maintenance of the Bloom's Syndrome Registry

46. GIESE, Roger W.
Northeastern University
5 R01 CA 35843-06
Ultratrace Analysis of DNA Lesions with Electrophoresis

47. GIESE, Roger W.
Northeastern University
5 U01 CA 43012-03
Chemical Digestion--GC/MS Analysis of DNA Adducts

48. GORBACH, Sherwoood L.
Tufts University
5 R37 CA 45128-03
Diet, Estrogens, & Breast Cancer

49. GRAHAM, Saxon
State University of New York, Buffalo
5 P01 CA 11535-17
Social Epidemiology of Cancer

50. GRUFFERMAN, Seymour
University of Pittsburgh
5 R01 CA 21244-08
The Epidemiology of Childhood Rhabdomyosarcoma

51. GRUFFERMAN, Seymour
University of Pittsburgh
7 R01 CA 39163-02
Epidemiology of Lymphomas in Unique Exposure Group

52. GRUFFERMAN, Seymour
University of Pittsburgh
5 R01 CA 47473-02
Case-Control Study of Hodgkin's Disease in Childhood

53. HANASH, Samir M.
University of Michigan, Ann Arbor
2 P01 CA 26803-08A1
Program Project: The Study of Human Mutation

54. HARRINGTON, David P.
Dana-Farber Cancer Institute
2 R01 CA 39929-04
Nonparametric Statistical Tests for Censored Cancer Data

55. HAYDEN, Cheryl L.
Yale University
1 R03 CA 45572-01
Estrogen Receptors in Normal & Neoplastic Colonic Mucosa

56. HILDRETH, Nancy G.
University of Rochester
5 R01 CA 19764-09
Human Radiation Carcinogenesis Study

57. HOFFMANN, Dietrich
American Health Foundation
5 R01 CA 40070-03
Biochemical Validation of Smoke Absorption by Infants

58. HOLFORD, Theodore R.
Yale University
5 R01 CA 30931-07
Systematic Analysis: Connecticut Cancer Incidence Trends

59. HOLLY, Elizabeth A.
Northern California Cancer Ctr.
5 R01 CA 34382-03
Melanoma, Oral Contraceptives Use & Reproductive Factors

60. HOLLY, Elizabeth A.
Northern California Cancer Ctr.
5 R01 CA 42440-02
Mutagenic Mucus in the Uterine Cervix of Smokers

61. HOLLY, Elizabeth A.
Northern California Cancer Ctr.
1 R01 CA 45614-01A1
Epidemiology of Non-Hodgkin's Lymphoma & Retroviral Tests

62. HOLMES, King K.
University of Washington
5 R01 CA 34493-05
Etiology & Natural History of Cervical Neoplasia

63. HSU, Jason C.
Ohio State University
5 R01 CA 41168-02
Multiple Comparisons with the Best Treatment

64. HULKA, Barbara S.
University of North Carolina
1 R03 CA 43781-01
Atypical Metaplasia as a Risk Factor for Lung Cancer

65. HULKA, Barbara S.
University of North Carolina
5 R03 CA 46437-02
The Role of Human Papillomavirus in Cervical Neoplasia

66. HULKA, Barbara S.
University of North Carolina
1 R03 CA 47076-01
Lipid Changes & the Incidence of Cancer

67. HUTCHISON, George B.
Harvard University
5 ROI CA 38071-04
Epidemiology of Non-Hodgkin's Lymphoma

68. JANGHORBANI, Morteza
University of Chicago
2 ROI CA 38943-04A1
Assessment of Selenium Status in Man

69. KAKAR, Faiz
Fred Hutchinson Cancer Res. Ctr.
1 UOI CA 48370-01
Carnitine as a Biochemical Marker of Fat Intake

70. KENNEDY, Susan
Poolman, Shih & Platton, Inc.
1 R43 CA 47688-01
Cancer Management Mapping System

71. KIRSCHNER, Marvin A.
Newark Beth Israel Med. Ctr.
5 ROI CA 39767-03
Androgen & Estrogen Dynamics in Obesity

72. KOLONEL, Laurence N.
University of Hawaii, Manoa
2 POI CA 33619-06
Epidemiologic Studies of Diet & Cancer in Hawaii

73. KOZIOL, James A.
Scripps Clinic & Res. Fdn.
5 ROI CA 41582-04
Topics in Biostatistics

74. LAGAKOS, Stephen W.
Harvard University
5 ROI CA 33041-06
Biostatistical Methods for Carcinogenicity Experiments

75. LAGAKOS, Stephen W.
Dana-Farber Cancer Institute
2 ROI CA 39640-04
Biostatistical Problems in Cancer Research

76. LE MARCHAND, Loic
University of Hawaii, Manoa
5 R29 CA 44503-02
Body Weight in Youth & Middle Age as Predictors of Cancer

77. LEONE, Fred C.
American Statistical Assoc.
1 R13 CA 46863-01
Environmetrics 87

78. LEVINE, Alexandra M.
University of Southern California
5 ROI CA 36301-03
Epidemiology, Immunology, & Virology in Homosexuals with PGL

79. LEY, Ronald D.
Lovelace Medical Foundation
1 UOI CA 48391-01
Stratospheric Ozone Depletion & Increased DNA Damage

80. LYNCH, Henry T.
Creighton University
5 ROI CA 41371-03
Hereditary Nonpolyposis Colorectal Cancer Resource

81. LYNCH, Henry T.
Creighton University
1 R01 CA 47429-01
Gene Probes in the FAMMM

82. MACK, Thomas M.
University of Southern California
5 R35 CA 42581-03
Epidemiologic Research in Cancer Etiology

83. MACMAHON, Brain
Harvard University
1 R01 CA 47305-01
Alcohol Consumption, Lactation, & Breast Cancer Risk

84. MATANOSKI, Genevieve M.
Johns Hopkins University
5 R01 CA 39764-02
Body Fat Distribution Type as an Endometrial Cancer Risk

85. MATANOSKI, Genevieve M.
Johns Hopkins University
1 R03 CA 45262-01
Recombinant Methods for Screening DNA Repair Proficiency

86. MC DOUGALL, James K.
Fred Hutchinson Cancer Res. Ctr.
5 P01 CA 42792-02
HPV: Biology, Clinical Significance, & Epidemiology

87. MEADOWS, Anna
Children's Hospital, Philadelphia
5 R01 CA 29275-06
The Epidemiology of Childhood Brain Tumors

88. MEHTA, Cyrus R.
Dana-Farber Cancer Institute
5 R01 CA 33019-07
Statistical Methods for Cancer Treatment & Prevention

89. MEHTA, Cyrus R.
Cytel Software Corporation
5 R44 CA 36681-03
Software for Exact Analysis of Categorical Data

90. MEHTA, Cyrus R.
Cytel Software Corporation
1 R43 CA 45901-01
Software for Longitudinal Data Analysis Related to Cancer Etiology

91. MELAMED, Myron R.
Memorial Hosp. for Can. & Allied Dis.
5 R01 CA 42830-03
Mathematical Model to Evaluate Lung Cancer Screening

92. MENCK, Herman R.
University of Southern California
5 R01 CA 35477-05
Case-Control Study of Gall Bladder Cancer

93. MILLER, Kenneth J.
Rensselaer Polytechnic Inst.
5 R01 CA 28924-05
Computer Assisted Analysis of Carcinogenicity

94. MIRVISH, Sidney S.
Univ. of Nebraska Med. Ctr.
5 U01 CA 43236-03
Establishing the Basics of the Nitrosoproline Test

95.	MODAN, Baruch Chaim Sheba Medial Center 1 R01 CA 45253-01	Neonatal Phototherapy & Childhood Malignancy
96.	MONSON, Richard R. Harvard University 5 R01 CA 22849-11	Second Cancers in Patients with Hodgkin's Disease
97.	MOOLGAVKAR, Suresh H. Fred Hutchinson Cancer Res. Ctr. 1 R01 CA 47658-01	Biomathematical Approaches to Cancer
98.	MORGAN, Timothy M. University of North Carolina 7 R23 CA 39575-04	Efficiency of Covariate Adjustment in the Cox Model
99.	MOSER, Royce University of Utah 5 P01 CA 34243-05	Epidemiologic & Biochemical Studies of Nutrition
100.	MUELLER, Nancy E. Harvard University 5 R01 CA 38450-03	Risk Factors for Human T-Cell Leukemia Virus Infection
101.	MUELLER, Nancy E. Harvard University 1 R01 CA 44578-01A1	The Epidemiology of "Classic" Kaposi's Sarcoma
102.	NAGAMANI, Manubai University of Texas Med. Br. 1 R01 CA 45181-01A1	Ovarian Steroids in Menopausal Women with Endometrial Cancer
103.	NEUGUT, Alfred I. Columbia University 5 R01 CA 37196-03	A Case-Control Study of Colorectal Polyps
104.	NEWCOMB, Polly Ann Univ. of Wisconsin Clin. Cancer Ctr. 1 R01 CA 47147-01	Alcohol Consumption, Lactation, & Breast Cancer Risk
105.	NEWELL, Guy R. University of Texas System Cancer Ctr. 2 R01 CA 34048-04	Nutrition Methodology for Epidemiological Cancer Studies
106.	NIERENBERG, David W. Dartmouth Medical School 5 R03 CA 46412-02	Seasonal & Diurnal Variation in Serum Carotenoids
107.	NOMURA, Abraham M. Kuakini Medical Center 5 R01 CA 33644-05	Cancer Epidemiology of the Migrant Japanese in Hawaii
108.	O'NEILL, Ian K. Internatl. Agency Res. Cancer 2 R01 CA 39417-03A1	In Vivo Microcapsule Monitoring of Carcinogens

109. OLSHEN, Richard A.
University of California, San Diego
5 R01 CA 41628-03
Biostatistics: Modeling & Inference

110. PAFFENBARGER, Ralph S.
Stanford University
5 R01 CA 44854-02
Physical Activity, Body Size, & Cancer Incidence

111. PAGANINI-HILL, Annlia
University of Southern California
5 R01 CA 32197-07
Estrogens & Vitamin A Role in Disease Prevention

112. PAGANO, Marcello
Harvard University
5 R01 CA 42982-02
Algorithms for Analyzing Discrete Data

113. PERERA, Frederica P.
Columbia University
5 R01 CA 39174-03
Carcinogen Dosimetry & Oncogene Activation in Human Subjects

114. PERERA, Frederica P.
Columbia University
5 U01 CA 43013-03
Biological Markers of Ethylene Oxide & Styrene Exposure

115. PETERS, Ruth K.
University of Southern California
2 R01 CA 35706-04
Completion of Epidemiologic Study of Anogenital Carcinoma

116. PETERS, Ruth K.
University of Southern California
5 R01 CA 36501-03
Case Control Study of Colon Carcinoma

117. PETERS, Ruth K.
University of Soluthern California
5 R01 CA 44401-02
Case-Control Study of Adenocarcinoma of the Cervix

118. PETRAKIS, Nicholas
Univ. of California, San Francisco
2 P01 CA 13556-16A1
Epidemiology & Natural History of Breast Cancer

119. PETRAKIS, Nicholas
Univ. of California, San Francisco
1 R01 CA 47288-01
Breast Cancer Incidence in Women with Abnormal Breast Cytology

120. PETREK, Jeanne A.
Memorial Hosp. for Cancer & Allied Dis.
1 R01 CA 47172-01
Adipose Fatty Acid Composition & Breast Cancer Risk

121. PIERCE, Donald A.
Oregon State University
5 R01 CA 27532-06
Statistical Methodology for Response-Time Data

122. PRESTON-MARTIN, Susan
University of Southern California
1 R01 CA 47082-01
Childhood Brain Tumors & N-Nitroso Exposures: U.S. Studies

123.	QIAN, Geng-Sun Shanghai Cancer Institute 1 R03 CA 47128-01	Aflatoxin Contamination of Commonly Eaten Foods
124.	RANDERATH, Kurt Baylor College of Medicine 5 U01 CA 43263-03	Detection & Measurement of Human DNA Adducts
125.	ROBISON, Leslie L. Univ. of Minnesota, Mnpls.-St.Paul 5 R01 CA 42479-02	Epidemiologic Study of Acute Leukemia in Infants
126.	RODRIGUEZ, Carlos C. State University of New York, Albany 5 R01 CA 41171-02	Maximum Entropy Densities
127.	ROSE, David P. American Health Foundation 5 R01 CA 39161-02	Hormone in Prostatic Fluid & Prostate Cancer Risk
128.	ROSE, David P. American Health Foundation 1 R03 CA 43694-01	EGF-Like Proteins in Breast Fluid
129.	ROSENBERG, Lynn Boston University Sch. Med. 1 R37 CA 45762-01A1	Case-Control Surveillance of Serious Illnesses & Drugs
130.	ROSS, Ronald K. University of Southern California 5 P01 CA 17054-13	USC Cancer Center Epidemiology & Biostatistics Unit: TAT
131.	ROSS, Ronald K. University of Southern California 5 R01 CA 36388-04	Case-Control Study of Multiple Myeloma
132.	ROSS, Ronald K. University of Southern California 5 R01 CA 43092-02	Dietary Factors in the Etiology of Cancer
133.	ROTHMAN, Kenneth J. University of Massachusetts Med. Sch. 2 R01 CA 38455-03	Case-Control Study of Laryngeal-Hypopharyngeal Cancer
134.	RYAN, Louise Dana-Farber Cancer Institute 1 R29 CA 48061-01	Biostatistical Topics in Carcinogenicity & Teratology
135.	SADOWSKI, James A. Tufts University 1 R03 CA 44551-01	Measurement of Dietary Sodium, Potassium, & Nitrate
136.	SANDLER, Robert S. University of North Carolina 1 R01 CA 44684-01A1	Risk Factors for Colon Adenomas

137. SHORE, Roy E.
New York University
5 R37 CA 43175-03
Follow-Up of Patients X-Irradiated for Scalp Ringworm

138. SHUKER, David E. G.
Internl. Agency Res. Cancer
1 U01 CA 48473-01
Excreted Alkyl Purines as Markers of in vivo DNA Damage

139. SHY, Carl M.
University of North Carolina
1 R03 CA 47864-01
Micronuclei in Bronchial Cells of Uranium Miners

140. SKOLNICK, Mark H.
University of Utah
5 R01 CA 28854-08
Genetic Epidemiology of Cancer in Utah Genealogies

141. SLATTERY, Martha L.
University of Utah Med. Ctr.
5 R01 CA 40060-03
Passive Smoking as a Cervical Cancer Risk Factor

142. SPEIZER, Frank E.
Brigham & Women's Hospital
5 R37 CA 40356-04
Prospective Study of Diet & Cancer in Women

143. STEBBINGS, James H.
University of Chicago
5 R01 CA 40071-02
Dose Interactions of Passive Smoking with Domestic Radon

144. STEMHAGEN, Annette
New Jersey State Dept. of Health
1 R01 CA 37744-01
Epidemiology of Lung Cancer among Women in New Jersey

145. STEVENS, Richard G.
Battelle Memorial Institute
5 R01 CA 41515-02
Iron Intake & Cancer Risk in NHANES I

146. STOCKWELL, Heather G.
University of South Florida
5 R29 CA 45513-02
Epidemiology of Lung Cancer in Non-Smoking Women

147. STORER, Barry E.
University of Wisconsin
5 R29 CA 45313-02
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148. STROM, Brian L.
University of Pennsylvania
3 R01 CA 35934-03S1
Biochemical Epidemiology of Biliary Tract Cancer

149. STRONG, Louise C.
University of Texas System Cancer Ctr.
5 R01 CA 27925-06
Genetic Etiology & Consequences of Childhood Cancer

150. STRONG, Louise C.
University of Texas System Cancer Ctr.
5 P01 CA 34936-05
A Mutational Model for Childhood Cancer

151. STRONG, Louise C.
University of Texas System Cancer Ctr.
2 R01 CA 38929-04
Genetic Epidemiology of Childhood Sarcoma

152. STRONG, Louise C.
University of Texas System Cancer Ctr.
1 R03 CA 47648-01A1
Genetic Epidemiology of Childhood Brain Tumors

153. SWIFT, Michael R.
University of North Carolina
5 R01 CA 14235-15
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154. SYME, S. Leonard
University of California, Berkeley
1 R03 CA 44445-01
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155. TANNER, Martin A.
University of Wisconsin, Madison
5 R01 CA 35464-05
Nonparametric Analysis of Censored Data

156. THOMAS, David B.
Fred Hutchinson Cancer Res. Ctr.
5 R01 CA 30022-04
Alcohol & Cancers of the Larynx & Esophagus

157. THOMAS, David B.
Fred Hutchinson Cancer Res. Ctr.
5 R01 CA 35653-04
Epidemiology of Male Breast Cancer

158. THOMAS, David B.
Fred Hutchinson Cancer Res. Ctr.
5 R37 CA 41530-03
Trace Elements & Cancers of Larynx, Esophagus & Mouth

159. THOMAS, Duncan C.
University of Southern California
5 R01 CA 42949-02
Time Related Factors in Cancer Epidemiology

160. THOMPSON, W. Douglas
Yale University
5 R01 CA 39477-03
An Epidemiologic Study of Multiple Primary Breast Cancer

161. TSIATIS, Anastasios A.
Dana-Farber Cancer Institute
5 R01 CA 36446-05
Early Stopping of Clinical Trials

162. VALANIS, Barbara G.
Kaiser Foundation Hospitals
1 R01 CA 47727-01
Health & Occupational Exposure to Anti-Cancer Drugs

163. VANDERLAAN, Martin
Lawrence Livermore Natl. Lab.
1 U01 CA 48446-01
Biochemical Measures of Exposure to Dietary Carcinogens

164. VAUGHAN, Thomas L.
Fred Hutchinson Cancer Res. Ctr.
1 R29 CA 46552-01
An Epidemiological Study of Nasopharyngeal Cancer

165.	WEI, Lee-Jen University of Michigan, Ann Arbor 5 R01 CA 45544-02	Nonparametric Statistical Methods in Cancer Research
166.	WEISS, Noel S. University of Washington 5 R35 CA 39779-04	Research in Cancer Epidemiology
167.	WESTHOFF, Carolyn L. Columbia University 1 R03 CA 47827-01	Ca-125 Levels in Blood of Normal Women
168.	WHITE, Emily Fred Hutchinson Cancer Res. Ctr. 5 R29 CA 44790-02	Epidemiology of Physical Activity & Colon Cancer
169.	WHITTEMORE, Alice S. Stanford University 2 R01 CA 23214-10	Effects of Multiple Exposures: Quantitative Aspects
170.	WHITTEMORE, Alice S. Stanford University 5 R01 CA 36503-04	Colo-Rectal Cancer in Chinese & Chinese-Americans
171.	WHITTEMORE, Alice S. Stanford University 5 R01 CA 45247-02	Reproductive Factors, Body Size, & Breast Cancer Risk
172.	WHITTEMORE, Alice S. Stanford University 1 R01 CA 47247-01	Combined Analysis of Ovarian Cancer Case-Control Data
173.	WIENCKE, John K. University of California 5 R01 CA 43764-02	Mutagen Sensitivity in High Breast Cancer Risk Patients
174.	WILLETT, Walter L. Harvard University 5 R01 CA 40429-04	Nutritional Determinants of Breast Cancer Risk
175.	WILLETT, Walter L. Brigham & Women's Hospital 5 R01 CA 42059-04	A Cohort Study of Trace Elements & Cancer in Women
176.	WOOLSON, Robert F. University of Iowa 5 R01 CA 39065-03	Epidemiologic Methods for Case-Control/Ecologic Studies
177.	WYNDER, Ernst L. American Health Foundation 5 P01 CA 32617-07	Interdisciplinary Studies in Cancer Epidemiology
178.	YU, Mimi C. University of Southern California 5 R01 40468-03	Salted Fish & Nasopharyngeal Carcinoma

179.	ZELEN, Marvin Dana-Farber Cancer Institute 5 R01 CA 23415-11	Statistical Models of Biomedical Phenomena
180.	ZIMMERMAN, Stuart O. University of Texas System Cancer Ctr. 2 R01 CA 11430-22	Biomathematics & Computing in a Cancer Institute

CONTRACTS ACTIVE DURING FY 88

Investigator/Institution/Contract		Title
181.	BOWEN, Kenneth A. Applied Logic Systems N44 CP 61026	User-Friendly Software for the Personal Computer (Bibliographic)
182.	DETELS, Roger University of California, Los Angeles N01 AI 32511	Natural History of AIDS in Homosexual Men
183.	IYPE, P. Thomas Biological Res. Facul. & Facil., Inc. N44 CP 85648	Antibody-Mediated Detection Systems for Acrolein: DNA Adducts
184.	KOKIKO, Elaine M. Moshman Associates, Inc. N01 CP 71017	Development of a Pre-1979 National Death Index
185.	LATER, Douglas W. Lee Scientific N44 CP 71086	Biochemical Monitoring of Pesticides & their Metabolites by Supercritical Fluid Chromatography
186.	MAURITSEN, Robert H. Statistics & Epidemiology Res. Corp. N44 CP 61035	User-Friendly Software for the Personal Computer (Statistical)
187.	POLK, B. Frank Johns Hopkins University N01 AI 32520	Natural History of AIDS in Homosexual Men
188.	RINALDO, Charles R., Jr. University of Pittsburgh N01 AI 32513	Natural History of AIDS in Homosexual Men
189.	SAILER, Peter Internal Revenue Service Y01 CP 50500	Test of the Usefulness of IRS Occupation Codes in Determining Mortality Differentials through the CWHS

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